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ORGANIC SYNTHESES

ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

VOLUME 62

1984

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* begin a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure, and to make the annual volumes more easily available to users. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Division of the American Chemical Society. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60–64 will be included in a new five-year version of the collective volumes of *Organic Syntheses* which will appear as *Collective Volume Seven* in the traditional hard cover format, after the appearance of annual volume 64. It will be available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

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NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is adopted. For example, both diethyl ether and ethyl ether are normally used. Since ethyl ether is the established *Chemical Abstracts* name for the 8th Collective Index, it has been used in this volume. The 9th Collective Index name is 1,1′-oxybisethane, which the Editors consider too cumbersome.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds that are of general interest, as well as procedures that illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should be checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yield should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point range should be reported, and for each liquid product the boiling-point range and refractive index should be included. In most instances it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, mass, or nuclear magnetic resonance spectra, and criteria of purity such as gas chromatographic data. In the event that any of the reactants are not commercially available at reasonable cost, their preparation should be described in as complete detail and in the same manner as the preparation of the product of major interest. The sources of the reactants should be described in the Notes section, and physical properties such as boiling point, index of refraction, and melting point of the reactants should be included except where standard commercial grades are specified.

Beginning with Volume 49, Methods of Preparation (Sec. 3) and Merits of the Preparation (Sec. 4) have been combined into Discussion (Sec. 3). This section should include descriptions of related and practical methods. Other published methods that have no practical synthetic value do not need to be mentioned. Those features of the procedure that recommend it for publication in *Organic Syntheses* should be cited (synthetic method of considerable scope, specific compound of interest not likely to be made available commercially, method that gives better yield or is less laborious than other methods, etc.). If possible, a brief discussion of the scope and limitations of the procedure as applied to other examples, as well as a comparison of the particular method with the other methods cited, should be included. If necessary to the understanding or use of the method for related syntheses, a brief discussion of the mechanism may be placed in this section. The present emphasis of *Organic Syntheses* is on model procedures rather than on specific compounds (although the latter are still welcomed), and the Discussion should be written to help readers decide on the value of the procedure in their research. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. An accompanying letter setting forth the features of the preparations that are of interest or value is helpful to the Board.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary.

JOHN R. JOHNSON

August 9, 1900–May 25, 1983

John Raven Johnson, known as Jack Johnson to all his friends, was a member of the first Board of Directors of *Organic Syntheses* when it was incorporated in the state of New York, December 11, 1939. He continued membership for about 20 years. Prior to this, Jack served for about 8 years on the Active Board of Editors, soliciting preparations and checking them. He was Editor-in-Chief of two annual volumes, Vol. XVI (1936) and Vol. XIX (1939). He also served on the Advisory Board of Editors until his death.

Jack Johnson was born in Chicago, August 9, 1900. He attended Lincoln School, Lane Technical High School and Lane Junior College and entered the University of Illinois (Urbana) in 1917. He received a B.S. in Chemistry in 1919; an M.S. in 1920 and the Ph.D. in 1922 just prior to his 22nd birthday. His Ph.D. research and thesis were carried out under the direction of Roger Adams. He received an American Field Fellowship for study abroad and spent two years at the College de France, working with Charles Maureau and Charles Dufraisse, two outstanding French organic chemists. Jack learned many new laboratory techniques, which he taught his research students and colleagues on his return to the states.

From 1924 to 1927, Jack Johnson served as instructor in organic chemistry at the University of Illinois (Urbana). Besides teaching and directing research problems for seniors and graduate students he collaborated with Roger Adams in publishing *Elementary Laboratory Experiments in Organic Chemistry*. It was first published in 1928 and had many revisions. This book, now in its 7th edition, has been edited in recent years by Charles F. Wilcox, one of Johnson's colleagues at Cornell University; *Adams and Johnson* was as well known in the U.S.A. as the classic *Gatterman–Wieland*.

In 1927, Jack Johnson became assistant professor at Cornell University thus starting a career which extended almost 40 years at that school. He restructured the courses in organic chemistry and developed a broad program of research. His enthusiasm and personal contributions led to his promotion to full professor in 1930 when he was barely 30 years old.

He was elected to the National Academy of Science in 1948 and was appointed to the endowed Todd Professorship at Cornell in 1952, a position he held until his retirement in 1965. In addition to his service on the Editorial Boards of

Organic Syntheses and *Organic Reactions,* Jack and his students published research papers on organo-boron compounds, furan derivatives, dienes, ketene derivatives, the structure of gliotoxin, and biosynthesis of isoprene derivatives.

As an outgrowth of an advanced Organic Chemistry course which Jack developed at Cornell, he prepared a 117 page chapter on *Modern Electronic Concepts of Valence,* which was published in Gilman's *Advanced Treatise on Organic Chemistry,* Volume II, 1938.

Jack was a consultant to the research division of duPont from 1937 to 1967 and encouraged the development of the great advances in polymer chemistry by Carothers, a friend from his Illinois days, and his co-workers at duPont.

During the period 1941–1945, Jack served on the NDRC and OSRD research projects connected with the war effort. He, with his collaborators at Cornell, contributed to the anti-malarial program and was a consultant to the penicillin program. He was a co-author with H. T. Clark and Sir Robert Robinson of the monograph *The Chemistry of Penicillin.* This volume summarized the work in the British and American Laboratories. In 1951 Jack served for a year in West Germany as special consultant to the U.S. State Department. For his wartime services he received the U.S. Medal of Merit and the *Medaille d'Honneur* of France. After his war service, Jack again took up his teaching and research at Cornell until he retired in 1965. A special symposium was held at Cornell in May of 1965 in honor of Jack Johnson's achievements.

Shortly after Jack moved to Cornell, he met Hope Anderson, A.B. Mt. Holyoke, 1923. They were married in 1929 and had a happy home, raising two sons, Keith and Leonard, in spite of the depression and war years. After retirement in 1965 Hope and Jack moved to their farm in Deer Valley, Townshend, Vermont. They enjoyed gardening and travel on passenger-carrying freighters to many parts of the world. In recent years, Jack developed emphysema and this ultimately led to his death on May 28, 1983. Jack Johnson played an important role in the growth of organic chemistry from 1922 to 1965. His many friends, students and colleagues remember him and honor him for his achievements.

January 1984 RALPH L. SHRINER

PREFACE

This annual volume continues the recent style of *Organic Syntheses* with emphasis on modern synthesis methodology. There are 28 checked procedures.

The first seven procedures are examples of metal-promoted processes and reflect the growing importance of organo-transition metal intermediates in organic synthesis. The synthesis of **Z-1-IODOHEXENE** demonstrates the copper-promoted carbo-metalation of acetylene starting from organo-lithium reagents, with high specificity in the geometry of the alkene. Extension of the Wacker process to a general conversion of terminal alkenes into methyl ketones is exemplified by the formation of **2-DECANONE.** The use of organocuprates is shown again through the conjugate addition–elimination reaction of enol phosphates of β-ketoesters to produce a **β-METHYL-α,β-UNSATURATED CARBOXYLIC ACID ESTER.** The value of lead(IV) compounds in activating electron-rich aromatic rings toward coupling with carbon nucleophiles is shown by the conversion of anisole directly to the *p*-(triacetoxylead) derivative and then coupling with a β-ketoester in pyridine, resulting in overall arylation of the β-ketoester. The coupling of main group organo-metal species with organic halides catalyzed by Pd(O) is one of the most powerful and general techniques for carbon–carbon bond formation. Included here are the coupling of a vinyl-alane with an allylic chloride to produce **α-FARNESENE** and the coupling of an aryl-lithium with *cis*-β-bromostyrene to give a ***cis*-1,2-DIARYLETHYLENE.** Both processes show the impressive selectivities characteristic of the general method. Nucleophilic addition to alkenes catalyzed by Pd(II) shows up again in the intramolecular addition of a sulfonamide to a mono-substituted alkene, producing a **DIHYDROPYRROLE** derivative. This sequence also demonstrates the conversion of a secondary hydroxyl to an amino group with inversion using diethyl azodicarboxylate and triphenylphosphine.

Seven procedures describe preparation of important synthesis intermediates. A two-step procedure gives **2-(HYDROXYMETHYL)ALLYLTRIMETHYLSILANE,** a versatile bifunctional reagent. As the acetate, it can be converted to a trimethylenemethane–palladium complex (*in situ*) which undergoes [3 + 2] annulation reactions with electron-deficient alkenes. A preparation of halide-free **METHYLLITHIUM** is included because the presence of lithium halide in the reagent sometimes complicates the analysis and use of methyllithium. Commercial samples invariably contain a full molar equivalent of bromide or iodide. **AZULENE** is a fundamental compound in organic chemistry; the preparation described in this volume is efficient and can be applied to substituted versions. The dienophile, **3-ACETYL-2(3H)-OXAZOLONE,** is an attractive intermediate for the synthesis of vicinal aminoalcohols with cis configuration. A new reagent, **2,4-BIS-(4-METHOXYPHENYL)-1,2,3,4-DITHIADIPHOSPHETANE-2,4-DISULFIDE,** is prepared in one step from anisole and P_4S_{10}, and serves in a general method of conversion of amides to thioamides, such as **N-METHYLTHIOPYRROLIDONE.** A powerful phosphorylating and acyl coupling reagent is **DIPHENYL PHOSPHORAZIDATE,** which is prepared in a simple way. Several quite different synthesis conversions have been developed with this reagent, and a general ring contraction procedure is exemplified by turning cyclododecanone into **CYCLOUNDECANECARBOXYLIC ACID.** The final specific reagent synthesis provides an unusual heterocyclic system, **THIETE 1,1-DIOXIDE** and **3-CHLOROTHIETE 1,1-DIOXIDE.** These reactive compounds are precursors of various heterocycles and of vinylsulfene, and have served as dienophiles in the Diels–Alder reaction.

Reduction of aryldiazonium salts with Ti(III) produces aryl radicals which couple efficiently with the β-position of α,β-unsaturated carbonyl compounds. The overall result is arylation of electron-deficient alkenes; **4-(*p*-CHLOROPHENYL)BUTAN-2-ONE** is obtained from 4-chlorobenzenediazonium chloride and methyl vinyl ketone. Remarkable selectivity in halogen–lithium exchange at low temperature allows formation of aryllithium reagents with chloroalkyl side chains. At higher temperatures direct ring closures occur, giving in this example **4,5-METHYLENEDIOXYBENZOCYCLOBUTENE.** The aryllithium can be intercepted by electrophiles such as a nitrile, leading to new ring systems. An example is the preparation of a **2-PHENYL-DIHYDROISOQUINOLINE.**

Titanium(IV) is a powerful but selective Lewis acid which can promote the coupling of allylsilanes with carbonyl compounds and derivatives. In the presence of titanium tetrachloride, benzalacetone reacts with allyltrimethylsilane by 1,4-addition to give **4-PHENYL-6-HEPTEN-2-ONE.** Similarly, the enol silyl ether of cyclopentanone is coupled with *t*-pentyl chloride using titanium tetrachloride to give **2-(tert-PENTYL)CYCLOPENTANONE,** an example of α-tert-alkylation of ketones.

Photochemical [2 + 2] cycloaddition is a powerful way to produce cyclobutanes, which, in turn, are reactive synthesis intermediates. N-Methylpyrrole adds aldehydes via [2 + 2] photocycloaddition to give transient oxetanes with high regioselectivity. Ring-opening produces 3-(α-hydroxyalkyl)pyrroles which are oxidized easily to 3-arylpyrroles, such as **3-BUTYROYL-1-METHYLPYRROLE.** With a special apparatus, ethylene is conveniently added to 3-methyl-

2-cyclohexenone to give **6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE.** Intramolecular [2 + 2] photocycloaddition of a diolefin is promoted by Cu(I). The specific example here carries an allylic hydroxyl group without interference and leads, after oxidation, to **3,3-DIMETHYL-cis-BICYCLO[3.2.0]-HEPTAN-2-ONE.**

It is well known that α,β-unsaturated ketones and aldehydes can be converted into β-bromoketals and acetals, which are generally useful synthesis intermediates. An improved procedure employs a small amount of dicinnamalacetone as indicator during addition of HBr to the unsaturated carbonyl compound. Both **2-(2-BROMOETHYL)-1,3-DIOXANE** (from acrolein) and **2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE** (from methyl vinyl ketone) are obtained in good yield on large scale. A general reduction method for converting quinones to arenes employs hydriodic acid and is particularly effective for large polynuclear aromatics, such as **BENZ[a]ANTHRACENE.**

An important biological process is the basis for a general coupling method of aldehydes into symmetrical acyloins, such as **BUTYROIN.** The key catalyst is 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, an analog of thiamin. Condensation of ketones and aldehydes with excess acetonitrile can be accomplished in a simple way to produce α,β-unsaturated nitriles. Cyclohexanone leads to **CYCLOHEXYLIDENEACETONITRILE** while benzaldehyde gives **CINNAMONITRILE.**

Cyanohydrin trimethylsilyl ethers are generally useful as precursors of ''carbonyl anion equivalents'' and as protected forms of aldehydes. Direct conversion of *p*-anisaldehyde into **O-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE** employs a convenient *in situ* generation of trimethylsilyl cyanide from chlorotrimethylsilane. A general synthesis of allenic esters is a variant of the Wittig reaction. Ethyl (triphenylphosphoranylidene)acetate converts propionyl chloride into **ETHYL 2,3-PENTADIENOATE.**

The Board of Editors welcomes both the submission of preparations for future volumes and suggestions for change that will enhance the usefulness of *Organic Syntheses*. Submitters are kindly asked to examine the instructions appearing before the Preface in this volume that describe the type of preparations we wish to receive and also the information to be included in each contribution. A Style Guide for preparing manuscripts is available from the Secretary to the Board, and submitters are requested to follow its instructions.

Professor Jeremiah P. Freeman, current Secretary to the Board, has carried on the voluminous correspondence with the submitters and the checkers behind the scenes and provided valuable guidance to the Editor-in-Chief. The *Chemical Abstracts* names and registry numbers in the appendix following each procedure were found and compiled by Dr. Theodora W. Greene, who also helped edit this volume. Special acknowledgment is due to Professor Carl R. Johnson, currently Treasurer of *Organic Syntheses, Inc.* for overseeing the publication of the soft-cover version of Volume 62. Finally, I would like to thank Mrs. Myra Martin at Notre Dame and Mrs. Beth Ebling at Princeton for their help in preparing the final edition.

MARTIN F. SEMMELHACK

Princeton, New Jersey
July 1984

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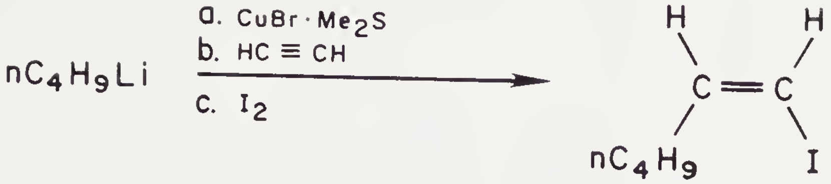
ORGANIC SYNTHESES

Z-1-IODOHEXENE

(1-Hexene, 1-iodo-, (Z)-)



Submitted by A. Alexakis, G. Cahiez, and J. F. Normant[1].

Checked by J. Gabriel, P. Knochel, and Dieter Seebach.

1. Procedure

A. *Preparation of an ether solution of lithium dibutylcuprate.* A 500-mL flask (Fig. 1) with a side arm is equipped with a magnetic stirring bar, rubber septum, and three-way stopcock, on top of which is attached a rubber balloon, D. A Pt-100-thermometer, E, is inserted into the flask through the septum (Note 1). The air in the flask is replaced by dry nitrogen (Note 2). The flask is charged with 10.8 g (0.0525 mol) of cuprous bromide-dimethyl sulfide complex (Note 3) and 100 mL of ether, then immersed in a bath at -50°C; 0.10 mol of n-butyllithium, ca. 1.6 M solution in hexane, (Note 4) is added dropwise, with stirring, via a syringe inserted through the rubber septum, at such a rate that the temperature of the reaction mixture does not exceed -20°C.

After the addition is complete, stirring is continued at -30°C for 10 min to produce a grey-blue or dark blue solution of the cuprate (Note 5).

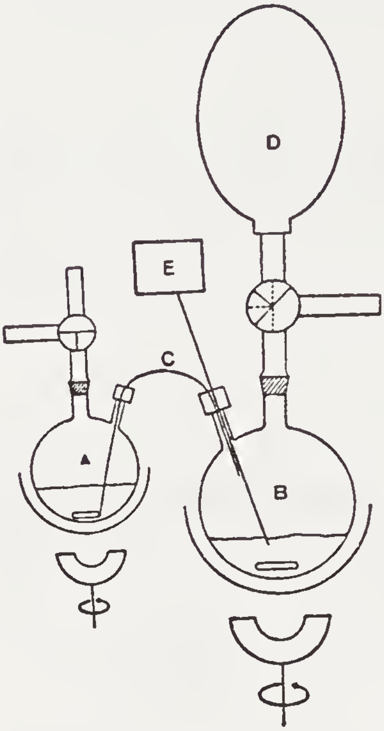


Figure 1

B. *Preparation of a solution of lithium di(Z-hexenyl)cuprate.* A needle connected to an acetylene supply (Note 6) is introduced through the rubber septum of the flask, with its end at least 1 cm below the surface of the cuprate solution. The stopcock is fully opened towards the balloon, the solution is cooled to -50°C, and 2.64 L (0.11 mol) of acetylene (Note 6) is bubbled into the stirred cuprate solution, the temperature of which should not rise above -25°C. The gas inlet is removed and the greenish solution is stirred at -25°C for 30 min.

C. Preparation of Z-iodohexene. A dry, 100-mL flask with a side arm is charged with 26.7 g (0.105 mol) of iodine, equipped with a stirring bar, three-way stopcock, and rubber septum, and flushed with argon as described above (Part A). The iodine is dissolved by introducing, with stirring, 30 mL of tetrahydrofuran through the septum with a syringe. Flask A, which contains the iodine solution, is connected to flask B, which contains the vinyl cuprate solution as shown in Figure 1. The cuprate solution is kept between -60° and -50°C while the iodine solution is pushed through the Teflon tubing, C. Then the cooling bath is removed and the temperature is allowed to rise to -10°C, whereupon a precipitate of copper(I) iodide is formed, and the mixture turns yellow. After 10 min at -10°C, a mixture of 100 mL of saturated aqueous ammonium chloride and 10 mL of saturated sodium bisulfite is added with vigorous stirring. The mixture is filtered by suction through 10 g of Celite on a sintered glass funnel (#3), the contents of the funnel are washed twice with 50 mL of ether, and the filtrate is separated into two layers (Note 7). The inorganic layer is washed twice with 50 mL of pentane, and the combined organic layers are washed with aqueous sodium bisulfite (Note 8) and saturated ammonium chloride solution, and dried over anhydrous $MgSO_4$. The solvents are removed by distillation through a 20-cm Vigreux column at atmospheric pressure. A spatula of copper powder is added to the residue, and the stirred mixture is distilled under reduced pressure through a 10-cm Vigreux column to give 13.5-15.5 g (65-75%) of Z-1-iodohexene, bp 47°C/(15 mm) (Notes 9 and 10).

2. Notes

1. The technique used here has been described previously by the checkers.[2] Instead, the submitters used a dry 500-mL, three-necked flask equipped with a variable speed mechanical stirrer, a 100-mL pressure-equalizing dropping funnel topped by a gas inlet and a Claisen head containing a low temperature thermometer (-70°C to +35°C), and a bubbler. A stream of nitrogen followed from the gas inlet.

2. This manipulation is described in detail in *Org. Synth.* **1971**, *51*, 39.

3. This complex[3] should be used when the organolithium is in solution in a hydrocarbon solvent. For organolithium reagents prepared in ether (see Note 4), the same complex may be used or, more conveniently, copper iodide (CuI) can be used. The CuI purchased from Prolabo or Merck & Company, Inc. may be used directly. Other commercial sources of CuI (Fluka, Aldrich Chemical Company, Inc., Alfa Products, Morton/Thiokol, Inc.) furnish a salt which affords better results when purified. 1 mol of CuI is stirred for 12 hr with 500 mL of anhydrous tetrahydrofuran, then filtered on a sintered glass funnel (#3), washed twice with 50 mL of anhydrous tetrahydrofuran, once with 50 mL of anhydrous ether and finally dried under reduced pressure (0.1 mm) for 4 hr.

4. n-Butyllithium was used as purchased from Aldrich Chemical Company, Inc., Fluka, or Metallgesellschaft (Frankfurt). Ethereal solutions of n-butyllithium may also be used. Other organolithium compounds are easily prepared in ether; the following is representative.

Under an atmosphere of argon, a solution of n-butyl bromide (137 g, 1 mol) in anhydrous ether (500 mL) is added with stirring to small chips of lithium containing 1-2% of sodium (15.5 g, 2.2 g-atom) in ether (150 mL). The reaction starts after the addition of about 40 mL of butyl bromide solution at room temperature. The temperature rises and the lithium metal becomes bright. If the reaction does not start, the addition of a small amount of 1,2-dibromoethane (1 mL) is often effective. Then the reaction mixture is cooled (-5°C to -10°C) and addition of the butyl bromide solution is continued slowly (about 4 hr). At the end of the addition, the solution is stirred for 2 hr at -5°C to -10°C; then the reaction mixture is allowed to warm to room temperature. After 2 hr, excess lithium metal is removed. For many purposes, the use of a clear solution, obtained after the reaction mixture has stood overnight at 0° to -5°C, is preferable. n-Butyllithium in ether can be stored under an argon atmosphere without decomposition for 15 days at 0°C or for 2 months at -15°C.

5. During all of the operations, the rate of stirring is adjusted to avoid splashing the wall of the flask; above -10°C, thermal decomposition of the cuprate occurs. This is indicated by the presence of a black suspension, which is also formed if a copper(I) salt of insufficient purity is used, or when oxygen gets into the reaction flask.

6. The proper volume of acetylene is measured with a water gasometer as described in *Org. Synth., Collect. Vol. 1* **1941**, 230, with two modifications: (a) Two traps immersed in an acetone-dry ice bath at -65°C are placed between the acetylene tank and the gasometer in order to remove acetone. (b) The washing bottles between the gasometer and the reaction flask are replaced by a drying tube (2 x 30-cm column packed with anhydrous $CaCl_2$).

The apparatus must be flushed with acetylene in order to remove all traces of oxygen. Acetylene dissolved in acetone is most appropriate. Acetylene obtained from tanks which contain solvents such as dimethylformamide (or other solvents) gave lower yields of carbocupration.

7. If a precipitate appears in the filtrate, filtration is repeated until two layers can be clearly distinguished.

8. A mixture of 10 mL of saturated sodium bisulfite and 50 mL of water is used. One or more washings with sodium bisulfite solution are necessary if iodine is present.

9. The sample thus obtained is >99% pure by GC analysis (3% OV 101 in a 2-m x 4-mm glass column, on Chromosorb G, with an injection temperature of 175°C, raised 100°C in 5 min, then 5°C/min).

10. The ^1H NMR spectrum of Z-1-iodohexene (in CCl_4) is as follows: δ: 6.12 (m, 2 H), 2.12 (m, 2 H, $-CH_2-C=$), 1.42 (m, 4 H, $-CH_2-$), 0.94 (m, 3 H).

3. Discussion

1-Iodoalkenes of the Z configuration are usually prepared by hydroboration of 1-iodoalkynes. The present method affords a product of higher configurational purity and constitutes an easier way to obtain such compounds in high yield, starting from less expensive reagents. In addition, the reaction can be performed easily on a larger scale (the submitters have prepared up to 1.8 mol of dialkenyl cuprate). The Z-1-iodo-1-alkenes shown in Table I have been prepared by the submitters.

TABLE I

EXAMPLES OF ALKENYL IODIDE PREPARATION FROM CARBO-CUPRATION

Entry	Organolithium	Product[a]	Yield(%)
1.	EtLi	EtCH=CHI	72
2.	n-C_5H_{11}Li	(n-C_5H_{11})CH=CHI	89
3.	n-C_7H_{15}Li	(n-C_7H_{15})CH=CHI	90
4.	EtCH=CHCH_2CH_2Li	EtCH=CHCH_2CH_2CH=CHI	79
5.	RO$(CH_2)_3$Li[b]	HO$(CH_2)_3$CH=CHI[c]	58
6.	RO$(CH_2)_8$Li[b]	HO$(CH_2)_8$CH=CHI[c]	70

[a] All alkenes, reactants and products, are Z. [b] R=CHMeOEt. [c] After acid hydrolysis.

This reaction illustrates a stereoselective preparation of (Z)-vinylic cuprates,[4,5] which are very useful synthetic intermediates. They react with a variety of electrophiles such as carbon dioxide,[5,6] epoxides,[5,6] aldehydes,[6] allylic halides,[7] alkyl halides,[7] and acetylenic halides;[7] they undergo conjugate addition to α,β-unsaturated esters,[5,6] ketones,[6] aldehydes,[6] and sulfones.[8] Finally they add smoothly to activated triple bonds[6] such as HC≡C-OEt, HC≡C-SEt, HC≡C-CH$(OEt)_2$. In most cases these cuprates transfer both alkenyl groups. The uses and applications of the carbocupration reaction have been reviewed recently.[9] The configurational purity in the final product is at least 99.9% Z in the above transformations.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Acetylene (8); Ethyne (9); (74-86-2)

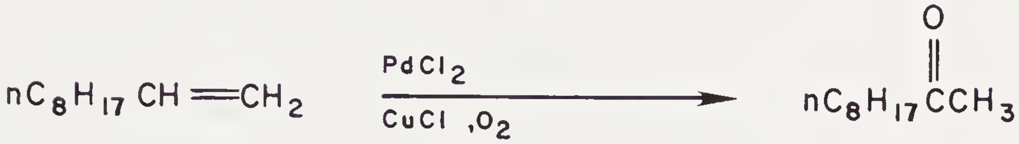
Iodine (8,9); (7553-56-2)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Z-1-Iodohexene: 1-Hexene, 1-iodo-, (Z)- (16538-47-9)

Copper iodide (8,9); (7681-65-4)

A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF METHYL KETONES FROM TERMINAL OLEFINS: 2-DECANONE



$$nC_8H_{17}CH{=}CH_2 \xrightarrow[CuCl\ ,O_2]{PdCl_2} nC_8H_{17}\overset{O}{\overset{\|}{C}}CH_3$$

Submitted by Jiro Tsuji, Hideo Nagashima, and Hisao Nemoto[1].

Checked by Edwin Vedejs, J. Gegner, and T. K. Mallman.

1. Procedure

A 100-mL, 3-necked, round-bottomed flask is fitted with a magnetic stirrer and a pressure-equalizing dropping funnel containing 1-decene (4.2 g, 30 mmol). The flask is charged with a mixture of palladium chloride (0.53 g, 3 mmol), cuprous chloride (2.97 g, 30 mmol) (Note 1) and aqueous dimethylformamide (DMF: H_2O = 7:1, 24 mL). With the other outlets securely stoppered and wired down, an oxygen-filled balloon (Note 2) is placed over one neck, and the flask is stirred at room temperature to allow oxygen uptake (Note 3). After 1 hr, 1-decene (4.2 g, 30 mmol) (Note 4) is added over 10 min (Note 5) using the dropping funnel, and the solution is stirred vigorously at room temperature under an oxygen balloon (Note 6). The color of the solution turns from green to black within 15 min and returns gradually to green. After 24 hr, the mixture is poured into cold 3N hydrochloric acid (100 mL) and extracted with five 50-mL portions of ether. The extracts are combined and washed successively with 50 mL of saturated sodium bicarbonate solution, 50 mL of brine, and then dried over anhydrous magnesium sulfate. After filtration, the solvent is removed by evaporation and the residue is distilled using a 15-cm Vigreux column to give 2-decanone as a colorless oil (3.0-3.4 g, 65-73%, bp 43-50°C/1 mm (Notes 7, 8).

2. Notes

1. Cupric chloride can be used, but it tends to chlorinate the products and cuprous chloride is preferable; reagent grade dimethylformamide (DMF) was distilled before use.

2. The balloon was bought at a toy shop; inflated volume was approximately 500 mL.

3. The initial black solution gradually turns green by oxygen absorption.

4. The sample of 1-decene was obtained from the Aldrich Chemical Company and distilled before use.

5. In cases where the alkene is soluble, up to 30% of the aqueous DMF can be mixed with the alkene to facilitate controlled addition. With 1-decene, DMF forms a two-phase mixture.

6. The reaction is slightly exothermic.

7. The first fraction (bp 30-40°C) contains decenes which are formed by palladium-catalyzed isomerization of 1-decene (indicated by a broad signal at δ 5.2-5.5 in the ^{1}H NMR spectrum).

8. The spectral properties of 2-decanone are as follows: ^{1}H NMR (CCl_4) δ: 2.37 (2 H, t, J = 7), 2.02 (3 H, s), 0.7-1.8 (15 H, complex); IR (neat) 1722 cm^{-1}.

3. Discussion

Methyl ketones are important intermediates for the synthesis of methyl alkyl carbinols, annulation reagents, and cyclic compounds. A common synthetic method for the preparation of methyl ketones is the alkylation of acetone derivatives, but the method suffers limitations such as low yields and lack of regioselectivity. Preparation of methyl ketones from olefins and acetylenes using mercury compounds is a better method. For example, hydration of terminal acetylenes using $HgSO_4$[2] gives methyl ketones cleanly. Oxymercuration of 1-olefins and subsequent oxidation with chromic oxide is another method.[3] Preparation of an epoxide from a 1-olefin and its rearrangement catalyzed by a cobalt catalyst to give methyl ketones has been reported briefly.[4]

Compared with these methods, the palladium-catalyzed oxidation of 1-olefins described here is more convenient and practical. The industrial method of ethylene oxidation to acetaldehyde using $PdCl_2$-$CuCl_2$-O_2 is the original reaction of this type.[5] The oxidation of various olefins has been carried out.[6,7,8,9]

Use of DMF as a solvent for the oxidation of 1-olefins has been reported by Clement and Selwitz.[6] The method requires only a catalytic amount of $PdCl_2$ and gives satisfactory yields under mild conditions. A small amount of olefin migration product is the only noticeable contaminant in the cases reported. The procedure can be applied satisfactorily to various 1-olefins with other functional groups. This useful synthetic method for the preparation of methyl ketones has been applied extensively in the syntheses of natural products such as steroids,[10] macrolides,[11,12] dihydrojasmone,[13] and muscone.[14] A comprehensive review article on the palladium-catalyzed oxidation of olefins has been published.[15]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

1-Decene (8,9); (872-05-9)

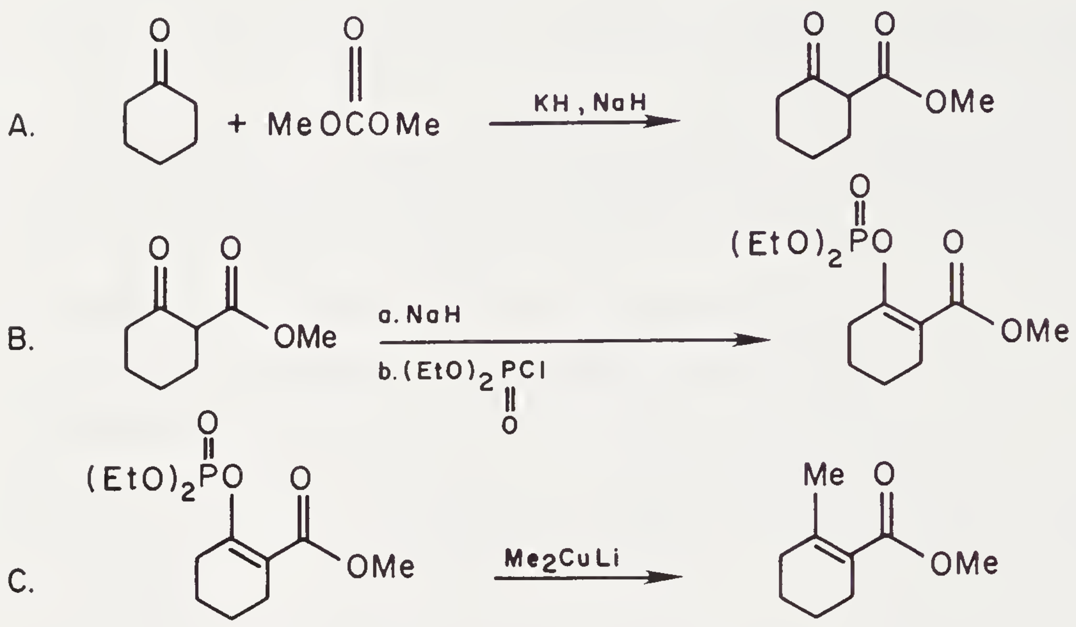
2-Decanone (8,9); (693-54-9)

Palladium chloride (8,9); (7647-10-1)

Cuprous chloride: Copper chloride (8,9); (7758-89-6)

β-ALKYL-α,β-UNSATURATED ESTERS FROM ENOL PHOSPHATES OF β-KETO ESTERS: METHYL 2-METHYL-1-CYCLOHEXENE-1-CARBOXYLATE

(1-Cyclohexene-1-carboxylic acid, 2-methyl, methyl ester)



Submitted by Margot Alderdice, F. W. Sum, and Larry Weiler[1].

Checked by Stephen P. Ashburn, Clark H. Cummins, and Robert M. Coates.

1. Procedure

A. Methyl 2-oxocyclohexanecarboxylate. A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, reflux condenser, and a pressure-equalizing dropping funnel bearing a nitrogen inlet (Note 1). The flask is flushed with nitrogen and charged with 18.02 g (0.20 mol) of dimethyl carbonate, 50 mL of anhydrous tetrahydrofuran, and 6.12 g (0.25 mol) of sodium hydride (Note 2). The suspension is stirred and heated to reflux temperature at which time the slow, dropwise addition of 7.80 g (0.080 mol) of cyclohexanone in 20 mL of dry tetrahydrofuran is begun. After 2 min, 0.306 g (0.0076 mol) of powdered potassium hydride (*Caution! Dry potassium hydride is pyrophoric.)* (Note 3) is added to initiate the reaction. The addition of cyclohexanone is continued over a period of 1 hr. The mixture is stirred and heated at reflux for another 30 min, cooled in an ice bath for 15-20 min, and hydrolyzed by slowly adding 75 mL of 3 M aqueous acetic acid. The contents of the flask are poured into 100 mL of aqueous sodium chloride, and the aqueous mixture is extracted with four 150-mL portions of chloroform. The organic layers are combined, dried with anhydrous sodium sulfate, and concentrated at room temperature with a rotary evaporator. Distillation of the residual liquid under reduced pressure gives 9.8-10.8 g (79-87%) of methyl 2-oxocyclohexanecarboxylate as a colorless liquid, bp 53-55°C (0.35 mm) (Note 4).

B. Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate. A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a gas inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is flushed with nitrogen and charged with 1.58 g (0.0329 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 5). The sodium hydride is freed from the mineral oil by washing with four 40-mL portions of anhydrous diethyl ether (Note 6) and withdrawing the supernatant solvent with a syringe, after which 120 mL of anhydrous ether is added. The mixture is stirred and cooled in an ice bath as 4.68 g (0.0300 mol) of methyl 2-oxocyclohexanecarboxylate (Note 7) in 10 mL of ether is added at a moderately rapid rate such that vigorous but controlled evolution of hydrogen occurs (Note 8). The resulting creamy suspension is stirred at 0°C for another 30 min after which 4.5 mL (5.37 g, 0.031 mol) of diethyl chlorophosphate (Note 9) is injected through the septum with a syringe. The ice bath is removed, the mixture is stirred at room temperature for an additional 3 hr, and 0.6 g of solid ammonium chloride is added. Stirring is continued for 30 min, and the salts are then separated by suction filtration through a medium porosity fritted glass funnel. Concentration of the filtrate under reduced pressure affords 8.18-8.63 g of the enol phosphate which is used in Part C without purification (Note 10).

C. Methyl 2-methyl-1-cyclohexene-1-carboxylate. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a pressure-equalizing addition funnel, and an inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is charged with 8.03 g (0.042 mol) of copper(I) iodide (Note 11) and 50 mL of dry diethyl ether (Note 6), flushed with nitrogen, and cooled in an ice bath. The mixture is stirred and cooled as 92.7 mL (0.084 mol) of 1.1 M methyllithium in diethyl ether (Note 12) is added quickly through the septum by means of a syringe. The resulting clear and colorless, or light tan, solution of lithium dimethylcuprate is then cooled in a carbon tetrachloride-dry ice slush bath maintained at -23°C (Note 13). A solution of 8.18-8.63 g (ca. 0.028-0.030 mol) of the enol phosphate in 35 mL of dry ether is added from the addition funnel over 5-10 min. Stirring and cooling are continued for 3 hr after which the dark purple solution is poured into a 1-L Erlenmeyer flask containing 75 mL of ice-cold 5% hydrochloric acid saturated with sodium chloride (Note 14). The mixture is stirred, or shaken vigorously, and cooled in an ice bath for 5-10 min to complete the hydrolysis. A 150-mL portion of 15% aqueous ammonia is added to the gray suspension and the mixture is swirled vigorously for a few min until the organic layer becomes clear and the aqueous layer turns bright blue. The mixture is transferred to a separatory funnel, the aqueous layer is withdrawn, and the organic phase is washed with 50 mL of 15% aqueous ammonia. The aqueous layers are combined and extracted with one 100-mL portion of ether. The combined ethereal layers are washed with two 50-mL portions of saturated sodium chloride, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. Distillation of the remaining 4.25-5.47 g of liquid in a short-path distillation apparatus affords 3.99-4.17 g (86-90% based on β-keto ester) of methyl 2-methyl-1-cyclohexene-1-carboxylate, bp 96-97°C (27 mm) (Notes 15, 16, and 17).

2. Notes

1. The glassware was dried in an oven at 125°C and assembled while warm.

2. Dimethyl carbonate is available from Aldrich Chemical Company, Inc. The checkers dried the tetrahydrofuran immediately before use by distillation from the sodium ketyl of benzophenone under a nitrogen atmosphere. The submitters purchased sodium hydride (50% oil dispersion) from Alfa Products, Morton/Thiokol, Inc. The checkers used 12.24 g of a 50% dispersion of sodium hydride in mineral oil obtained from the same supplier. The dispersion was washed with three portions of pentane to remove the mineral oil and the remaining sodium hydride was allowed to dry under nitrogen.

3. The submitters used a 35% dispersion of potassium hydride in mineral oil supplied by Alfa Products, Morton/Thiokol, Inc.; the mineral oil was separated by washing the dispersion with five portions of dry hexane. The checkers used a 25% dispersion of potassium hydride in mineral oil obtained from the same source but without removing the mineral oil. The oil remained in the distillation pot when the product was distilled.

4. A boiling point of 68°C (0.8 mm) and a melting point of 25°C have been reported for methyl 2-oxocyclohexanecarboxylate.[2] The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 1745, 1715, 1615; ^1H NMR ($CDCl_3$) δ: 1.62 (m, 4 H, two CH_2), 2.22 (m, 4 H, two CH_2), 3.37 (t, 0.25 H, J = 7 Hz, CH at C-2 in keto form), 3.74 (s, 3 H, CH_3), 12.10 (s, 0.75 H, enol OH).

5. The sodium hydride-mineral oil dispersion was purchased from Alfa Products, Morton/Thiokol, Inc.

6. Diethyl ether was dried by the submitters by refluxing over lithium aluminum hydride and was distilled immediately before use. The checkers distilled diethyl ether from the sodium ketyl of benzophenone before use.

7. A mixture of methyl and ethyl 2-oxocyclohexanecarboxylate, available from Aldrich Chemical Company, Inc., may also be used. The product obtained is a mixture of methyl and ethyl 2-methylcyclohexene-1-carboxylates.

8. No gas evolution was observed by the checkers in some runs in which an older lot of sodium hydride was used. In this case, the cooling bath was removed and the mixture was allowed to stir at room temperature until the bubbling ceased.

9. Diethyl chlorophosphate, supplied by Aldrich Chemical Company, Inc., was used by the submitters without purification and was handled in a glove bag under an atmosphere of dry nitrogen in a well-ventilated hood. The reagent was distilled and stored under nitrogen by the checkers. Aliquots were withdrawn with a syringe as needed.

10. The spectral properties of the enol phosphate are as follows: IR ($CHCl_3$) cm^{-1}: 1715, 1660, 1290, 1030; 90 MHz ^1H NMR ($CDCl_3$) δ: 1.3-1.9 (m, 4 H, CH_2CH_2), 1.35 (t, 6 H, J = 7 Hz, OCH_2CH_3), 2.3 (m, 4 H, allylic CH_2), 3.68 (s, 3 H, OCH_3), 4.15 (quintet, 4 H, J = 7 Hz, OCH_2CH_3).

11. Copper(I) iodide, supplied by either MC and B Manufacturing Chemists or Fisher Scientific Company, was purified by recrystallization from water saturated with potassium iodide.[3,4] The wet powder was washed successively with ethanol, acetone, and ether, and dried by heating overnight at 100°C in an evacuated drying pistol containing phosphorus pentoxide.[4a,5] The submitters advise that the compound should not be dried by heating in air.[5] When oven-dried copper(I) iodide was used in this procedure, the yield of product was somewhat lower (77-88%) and as much as 10-20% of 1-acetyl-2-methylcyclohexene was formed. It is probable that the presence of small amounts of copper(II) impurities is responsible for the increased proportion of this by-product.[4b,6] Purified copper(I) iodide may be stored under nitrogen without change for several months.[4a]

12. Ethereal methyllithium (as the lithium bromide complex) was obtained by the submitters from Aldrich Chemical Company Inc. The checkers used 1.19 M methyllithium-lithium bromide complex in ether supplied by Alfa Products, Morton/Thiokol, Inc. The concentration of the methyllithium was determined by titration with 1.0 M tert-butyl alcohol in benzene using 1,10-phenanthroline as indicator.[7] The submitters report that ethereal methyllithium of low halide content purchased from Alfa Products, Morton/Thiokol, Inc., gave similar results.

13. The coupling reaction between lithium dimethylcuprate and acyclic enol phosphates must be carried out between -47 and -98°C for stereoselective formation of β-methyl-α,β-unsaturated esters.

14. The submitters have found that the reaction may also be hydrolyzed with a solution of 60 mL of saturated ammonium chloride and 15 mL of concentrated aqueous ammonia. The ethereal layer is then washed with 15% aqueous ammonia until the aqueous layer is no longer blue.

When lithium di-n-butylcuprate is used, the yields are often improved by adding 1-bromobutane to the reaction mixture before hydrolysis with aqueous ammonium chloride.

15. The product exhibits the following spectral properties: IR ($CHCl_3$) 1720, 1640, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.3-1.7 (m, 4 H, CH_2CH_2), 1.8-2.4 (m, 4 H, allylic CH_2), 1.97 (s, 3 H, CH_3), 3.69 (s, 3 H, OCH_3); MS (70 eV) m/e (assignment, rel intensity): 154 (M^+, 50%), 95 ($-CO_2CH_3$, 100%).

16. The purity of the product was determined by the checkers by GLC analysis using the following column and conditions: 3-mm by 1.8-m column, 5% free fatty acid phase (FFAP) on acid-washed chromosorb W (60-80 mesh) treated with dimethyldichlorosilane, 90°C (1 min) then 90° to 200°C (15°C per min). The chromatogram showed a major peak for methyl 2-methyl-1-cyclohexene-1-carboxylate preceded by two minor peaks for methyl 1-cyclohexene-1-carboxylate and 1-acetyl-2-methylcyclohexene. The areas of the two impurity peaks were 5-6% and 0.5-2% that of the major peak. The purity of the product seems to depend upon careful temperature control during the reaction. The total amount of the two impurities was 14-21% in runs conducted at about -15 to -20°C or at temperatures below -23°C.

17. The submitters purified the product by distillation in a Kugelrohr apparatus with an oven temperature of 85-88°C (20 mm) and obtained 3.80-3.85 g (88-89%). The purity of the product was 93-96% according to GLC analysis. The major impurity (2-6%) was 1-acetyl-2-methylcyclohexene.

The product may also be purified by flash chromatography[8] using 19/1 (v/v) petroleum ether, (bp 30-60°C)/ethyl acetate as eluant. A column of 2-cm diameter was packed to a height of 25 cm with Kieselgel 60 (230-400 mesh) supplied by BDH Chemicals Ltd. In one run chromatography of 4.19 g of crude product afforded 3.70 g (88%) of the α,β-unsaturated ester which was completely free of the more polar by-product, 1-acetyl-2-methylcyclohexene. However, the checkers found that the other by-product, methyl 1-cyclohexene-1-carboxylate, is not readily separated by flash chromatography.

3. Discussion

This procedure illustrates a new method for the preparation of β-alkyl-α,β-unsaturated esters by coupling lithium dialkylcuprates with enol phosphates of β-keto esters.[9] The procedure for the preparation of methyl 2-oxocyclohexanecarboxylate described in Part A is based on one reported by Ruest, Blouin, and Deslongchamps.[2] Methyl 2-methyl-1-cyclohexene-1-carboxylate has been prepared by esterification of the corresponding acid with diazomethane[10] and by reaction of methyl 2-chloro-1-cyclohexene-1-carboxylate with lithium dimethylcuprate.[11]

The formation of β-alkyl-α,β-unsaturated esters by reaction of lithium dialkylcuprates or Grignard reagents in the presence of copper(I) iodide, with β-phenylthio-,[12,13] β-acetoxy-,[14,15] β-chloro-,[11,16] and β-phosphoryloxy-α,β-unsaturated esters[9] has been reported. The principal advantage of the enol phosphate method is the ease and efficiency with which these compounds may be prepared from β-keto esters. A wide variety of cyclic and acyclic β-alkyl-α,β-unsaturated esters has been synthesized from the corresponding β-keto esters.[9] However, the method is limited to primary dialkylcuprates. Acyclic β-keto esters afford (Z)-enol phosphates which undergo stereoselective substitution with lithium dialkylcuprates with predominant retention of stereochemistry (usually > 85-98%). It is essential that the cuprate coupling reaction of the acyclic enol phosphates be carried out at lower temperatures (-47 to -98°C) to achieve high stereoselectivity. When combined with the γ-alkylation of methyl acetoacetate dianion,[17] this method provides a facile means of isoprenoid chain extension.[18] The procedures have been employed to advantage in syntheses of (E,E)-10-hydroxy-3,7-dimethyldeca-2,6-dienoic acid,[18a] latia luciferin[18b] and mokupalide.[18c] β-Diketones may be converted to β-alkyl-α,β-unsaturated ketones in a similar manner.[9]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 2-methyl-1-cyclohexene-1-carboxylate: 1-Cyclohexene-1-carboxylic acid, 2-methyl-, methyl ester (9); (25662-38-3)

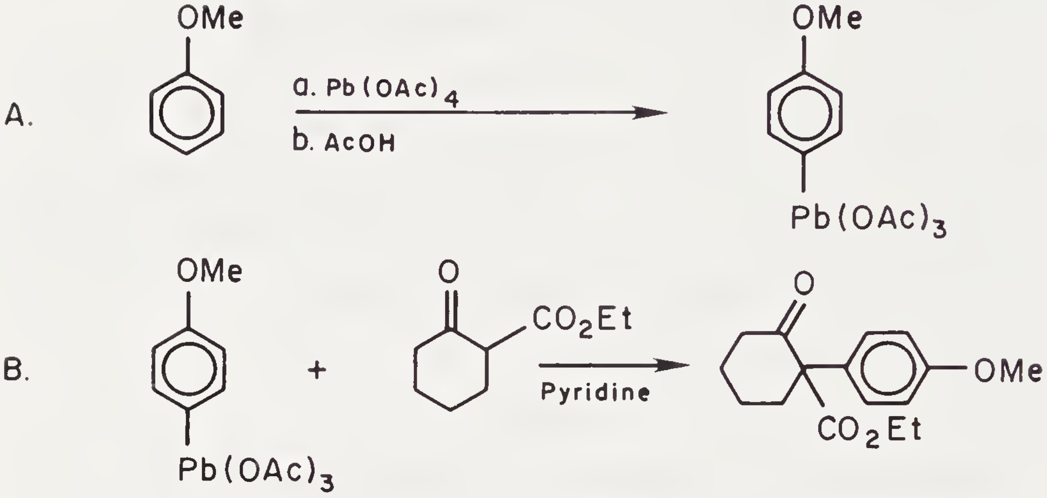
Dimethyl carbonate: Carbonic acid, dimethyl ester (8,9); (616-38-6)

Methyl 2-oxocyclohexanecarboxylate: Cyclohexanecarboxylic acid, 2-oxo-, methyl ester (9); (41302-34-5)

Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester (8,9); (814-49-3)

Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate: 1-Cyclohexene-1-carboxylic acid, 2-[(diethoxyphosphinyl)oxy]-, methyl ester (10); (71712-64-6)

THE C-ARYLATION OF β-DICARBONYL COMPOUNDS; ETHYL 1-(p-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE



Submitted by Robert P. Kozyrod and John T. Pinhey[1].

Checked by M. F. Semmelhack and David Ziering.

1. Procedure

A. *p-Methoxyphenyllead triacetate.* A 1-L Erlenmeyer flask, equipped with a magnetic stirring bar, is charged with 50 g (0.11 mol) of lead tetraacetate (Note 1), chloroform (200 mL), and 140 g (1.09 mol) of dichloroacetic acid (Note 2). To this solution is added 16 g (0.15 mol) of anisole (Note 3), and the mixture is stirred at 25°C until lead tetraacetate can no longer be detected (Note 4). The reaction mixture is washed with water (2 x 250 mL) and the chloroform solution is treated with 1.5 L of hexane (Note 5). The yellow precipitate (44 g) is collected by suction filtration and stirred with a mixture of glacial acetic acid (250 mL) and chloroform (200 mL) for 1 hr.

The chloroform solution is washed with water (2 x 250 mL) and stirred with glacial acetic acid (250 mL) for 1 hr (Note 6). The solution that results is washed with water (2 x 250 mL), and the chloroform phase is treated with 1.5 L of hexane and kept at 2°C for 48 hr. The material which precipitates is collected and dried at 0.1 mm in a desiccator (calcium chloride) for 5 hr to give p-methoxyphenyllead triacetate (20-22 g, 35-40%) as pale yellow crystals, mp 138-139°C (Note 7). The product may be kept for at least 3 weeks if stored at 2°C in a sealed container.

B. Ethyl 1-(p-methoxyphenyl)-2-oxocyclohexanecarboxylate. A 250 mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 22.2 g (45 mmol) of p-methoxyphenyllead triacetate, 10.8 g (135 mmol) of pyridine (Note 8), and 70 mL of chloroform (Note 9). To this solution is added 7.0 g (41 mmol) of ethyl 2-oxocyclohexanecarboxylate (Note 10), a calcium chloride drying tube is put in place, and the mixture is stirred at 40°C (Note 11).

After 24 hr, the reaction mixture is diluted with chloroform (80 mL), and washed with water (150 mL) and 3 M sulfuric acid (2 x 150 mL). The water and sulfuric acid washings are each washed (Note 12) with 100 mL of chloroform. The combined chloroform extracts are washed with water (2 x 250 mL), dried with magnesium sulfate, and the solvent removed to give an orange-colored oil (10.3 g) which slowly crystallizes on standing. Crystallization from hexane (Note 5) gives 9.4 g (82%) of ethyl 1-(p-methoxyphenyl)-2-oxocyclohexanecarboxylate, mp 49-50°C.

2. Notes

1. Lead tetraacetate from Merck & Company, Inc. was used. Acetic acid was removed from the reagent at 0.1 mm for 24 hr, in the dark, in a desiccator containing potassium hydroxide pellets.

2. Dichloroacetic acid from Merck & Company, Inc. was used without further purification.

3. Anisole from Fluka AG was distilled before use.

4. A few drops of reaction mixture were shaken with water. A brown precipitate of PbO_2 indicates the presence of unreacted lead tetraacetate. For the quantities given, a reaction time of 1 hr at 15-20°C is adequate.

5. Hexanes, bp 60-69°C, certified by Fisher Scientific Company were used.

6. A second metathesis with glacial acetic acid is carried out to ensure complete conversion of the oligomer into the product.

7. It has been found that the yield of product is generally higher when the reaction is performed on a smaller scale. Reactions carried out on approximately one third of the above scale have given yields of approximately 60%.

8. Pyridine from Merck & Company, Inc. was distilled and stored over potassium hydroxide pellets.

9. Chloroform was dried over calcium chloride and distilled prior to use.

10. The ethyl 2-oxocyclohexanecarboxylate used was Fluka AG practical grade, and was distilled (bp 105-108°C/12 mm) before use.

11. The submitters report that after approximately 1 hr some lead(II) acetate is deposited as an orange-red gum which may temporarily restrict the motion of the stirring bar; this was not observed by the checkers. The material generally crystallizes after a short period as a white solid.

12. These washings are extracted separately in order to minimize formation of solid lead(II) sulfate.

3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α-arylation of β-dicarbonyl compounds by means of an aryllead triacetate under very mild conditions. Although the first synthesis of an aryllead triacetate was reported relatively recently, a wide range of these compounds can now be readily prepared.[2] The most direct route to these compounds is plumbation of an aromatic compound with lead tetraacetate, and in the procedure reported here p-methoxyphenyllead triacetate has been prepared in this way. It may also be obtained by reaction of the diarylmercury with lead tetraacetate,[3] a longer, but more general method of synthesis of aryllead triacetates.

The first synthesis of p-methoxyphenyllead triacetate by direct plumbation was reported by Harvey and Norman,[4] who obtained the compound in 24% yield by heating anisole and lead tetraacetate in acetic acid at 80°C for 4 days. Recently it has been found[2] that a much faster reaction and higher yield of aryllead compounds can be achieved by use of a haloacetic acid in place of acetic acid, and this has allowed the synthesis of a greater range of aryllead triacetates by direct plumbation. The improved reaction rate is presumably due to an increase in electrophilicity of lead when acetate is exchanged for a more electron-withdrawing ligand. The choice of the haloacetic acid depends on the reactivity of the aromatic substrate; thus while dichloroacetic acid has been found best for the plumbation of anisole, trichloroacetic acid is preferred in the case of toluene and biphenyl.[2]

Aryllead tricarboxylates have been shown to be intermediates in two new routes to phenols,[5,6] and to have considerable potential as reagents for the C-arylation of carbon acids which are more acidic than diethyl malonate. A study of their reactions with β-diketones,[7] β-keto esters,[8] and Meldrum's acid and its derivatives[9] has established that such compounds, which contain only one replaceable hydrogen, undergo smooth arylation in high yield under the conditions outlined in this procedure. Compounds which contain two replaceable hydrogens are less predictable in their behavior. When a 1:1 ratio of substrate to aryllead compound is used, dimedone gave only diarylated product in high yield, while ethyl acetoacetate gave both mono- and di-arylated products in only moderate yield.

Recently it has been shown that triphenylbismuth carbonate[10] and pentaphenylbismuth[11] can be used to achieve a similar arylation of β-dicarbonyl compounds. These reagents also react under very mild conditions and yields are generally high. Prior to the introduction of the organolead and organobismuth reagents, the most promising procedure for arylation of β-dicarbonyl compounds involved reaction of the enolate anion with a diaryliodonium salt, usually at 80-100°C.[12] Although only a limited range of substrates has been examined, it would appear that yields are only moderate, and in the case of dimedone a mixture of mono-, di-, and O-arylated products is produced. A further method, which has obvious limitations, involves the copper-catalyzed substitution of bromine in 2-bromobenzoic acids by the enolate anion of a β-dicarbonyl compound.[13]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

p-Methoxyphenyllead: Plumbane, triacetoxy(p-methoxyphenyl)- (8); Plumbane, tris(acetyloxy)(4-methoxyphenyl)- (9); (18649-43-9)

Lead tetracetate: Acetic acid, lead (4+) salt (8,9); (546-67-8)

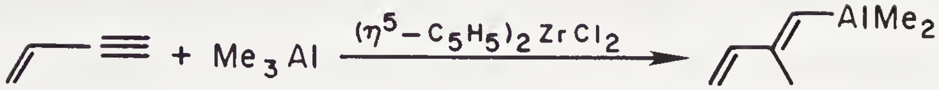
Anisole (8); Benzene, methoxy- (9); (100-66-3)

Ethyl 2-oxocyclohexanecarboxylate: Cyclohexanecarboxylic acid, 2-oxo-, ethyl ester (8,9); (1655-07-8)

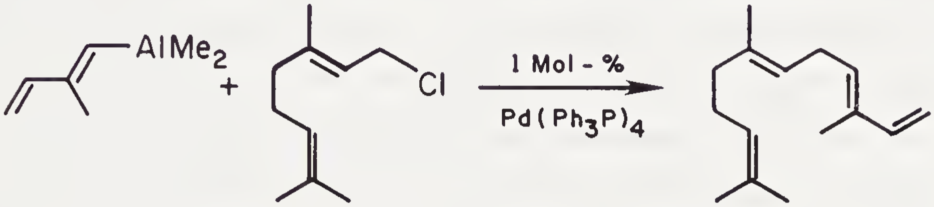
PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY ALLYLATION OF ALKENYLALANES: α-FARNESENE

(1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-)

A.



B.



Submitted by Ei-ichi Negishi[1] and Hajime Matsushita[2].

Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

Caution! Trimethylalane (Note 1) is highly pyrophoric. It must be kept and used under a nitrogen atmosphere.

A. (E)-(2-Methyl-1,3-butadienyl)dimethylalane. An oven-dried, 1-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an outlet connected to a mercury bubbler is charged with 7.01 g (24 mmol) of dichlorobis(η^5-cyclopentadienyl)zirconium (Note 2) and flushed with nitrogen. To this are added sequentially at 0°C 100 mL of 1,2-dichloroethane (Note 3), 12.48 g (120 mmol) of a 50% solution of 1-buten-3-yne in xylene (Note 4), and 120 mL (240 mmol) of a 2 M solution of trimethylalane in toluene (Note 1). The reaction mixture is stirred for 12 hr at room temperature and used in the next step without further treatment (Note 5).

B. (3E, 6E)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (α-farnesene). To the solution of (E)-(2-methyl-1,3-butadienyl)dimethylalane prepared above are added 17.25 g (100 mmol) of geranyl chloride (Note 6) and 1.15 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 7) dissolved in 100 mL of dry tetrahydrofuran (Note 8), while the reaction temperature is controlled below 25-30°C with a water bath. After the reaction mixture is stirred for 6 hr at room temperature, 250 mL of 3 N hydrochloric acid is slowly added at 0°C. The organic layer is separated and the aqueous layer is extracted twice with pentane. The combined organic layer is washed with water, saturated aqueous sodium bicarbonate, and water. After the organic extract is dried over anhydrous magnesium sulfate, the solvent is removed thoroughly using a rotary evaporator (15-20 mm), and the crude product is passed through a short (15-20 cm) silica gel column (60-200 mesh) using hexane as an eluent (Note 9). After the hexane is evaporated using a rotary evaporator, the residue is distilled using a 12-cm Vigreux column to give 16.70 g (83% based on geranyl chloride) of α-farnesene as a colorless liquid, bp 63-65° (0.05 mm) (Note 10).

2. Notes

1. The submitters used trimethylalane available in a cylinder from Ethyl Corporation. Both neat trimethylalane and its 2 M solution in toluene gave comparable results. The toluene solution of trimethylalane is also available from Aldrich Chemical Company.

2. The submitters used dichlorobis(η^5-cyclopentadienyl)zirconium available from Aldrich Chemical Company. This chemical is sufficiently air-stable to be handled in air.

3. The 1,2-dichloroethane available from Aldrich Chemical Company was distilled from phosphorus pentoxide before use. Although less effective, dichloromethane may also be used in the carbometallation step.

4. The submitters used a 50% solution of 1-buten-3-yne in xylene, available from Chemical Samples Company. For transferring this solution, the following procedure may be recommended. An ampule containing the solution is cooled with an ice-salt bath, opened, and capped with a rubber septum. A weighed measuring flask capped with a rubber septum is cooled with the ice-salt bath. To this is introduced the cooled solution by means of a double-tipped needle, and the weighed solution is then introduced to the reaction flask by means of a double-tipped needle.

5. The reaction mixture containing (E)-(2-methyl-1,3-butadienyl)dimethylalane may be stored at room temperature for at least a few days. Although it appears to be stable at room temperature for a much longer period of time, its thermal stability has not been carefully determined. The cross-coupling reaction in Section B should require only one equivalent of the alkenylalane, and its yield by gas chromatographic examination is 90-100%. It is practical, however, to use ca. 20% excess of 1-buten-3-yne for preparing the alkenylalane so as to achieve a high-yield conversion of geranyl chloride into α-farnesene.

6. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, with carbon tetrachloride and triphenylphosphine according to an Organic Syntheses procedure (Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, *54*, 63).

7. Tetrakis(triphenylphosphine)palladium was prepared by treating palladium chloride, available from Matthey Bishop, Inc., with hydrazine hydrate in the presence of triphenylphosphine according to an Inorganic Syntheses procedure.[3] The submitters used a freshly prepared, shiny yellow, crystalline sample of the palladium complex. On standing for an extended period of time (> a few weeks), its color gradually darkens. Even such samples are effective in many palladium-catalyzed cross-coupling reactions,[4] but have not been tested in this reaction. Tetrakis(triphenylphosphine)palladium is also available from Aldrich Chemical Company.

8. Tetrahydrofuran available from Aldrich Chemical Company was distilled from sodium and benzophenone.

9. The main purpose of this filtration is to remove traces, if any, of palladium-containing compounds that might induce undesirable transformations, such as isomerization and polymerization, during the subsequent distillative workup.

10. The submitters reported bp 73-75°C (0.05 mm). Gas chromatographic examination of the reaction mixture with a hydrocarbon internal standard indicates that α-farnesene is formed in 98% yield, based on geranyl chloride, essentially as a single product (>98%). The product obtained by this procedure shows the following properties: n_D^{23} 1.4977; IR (neat) cm^{-1}: 3080(w), 2960(s), 2900(s), 1664(w), 1635(m), 1601(m), 981(m), 883(s); ^1H NMR [$CDCl_3$, $(CH_3)_4Si$] δ: 1.59 (s, 3 H), 1.63 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 2.03 (m, 4 H), 2.82 (t, J = 6, 2 H); ^{13}C NMR [$CDCl_3$, $(CH_3)_4)Si$] δ: 11.62, 16.07, 17.63, 25.69, 26.89, 27.35, 39.88, 110.37, 122.36, 124.50, 131.10, 131.74, 133.79, 135.55, 141.69.

3. Discussion

This procedure for the synthesis of α-farnesene[5] is representative of the palladium-catalyzed stereo- and regiospecific coupling of allylic derivatives with alkenyl- and arylmetals.[6] The use of neryl chloride in place of geranyl chloride gives the 6-Z isomer of α-farnesene in 77% yield (>98% isomeric purity).[6] The high stereo- and regiospecificity (>98%) has been observed only with γ,γ-disubstituted allylic electrophiles. With γ-monosubstituted allylic derivatives, varying amounts of stereo- and regio-isomers have been observed.[7]

Various allyl derivatives, such as those containing acyloxy, dialkylaluminoxy, and trialkylsilyloxy groups, also react with alkenylalanes in the presence of a palladium-phosphine catalyst,[7] and the synthesis of α-farnesene has been achieved by using geranyl acetate. Although the observed yields are ca. 20% lower than those observed with geranyl chloride, a careful comparison of the two derivatives has not been performed. In general, the order of reactivity of various leaving groups is: $-Cl > -OAc > -OPO(OR)_2 > -OSiR_3$.

In addition to alkenylalanes, readily obtainable by either hydroalumination[8] or carboalumination[9] of alkynes, alkenylzirconium derivatives,[6,10] obtainable by hydrozirconation[11] of alkynes, undergo a related alkenyl-allyl coupling reaction. In a related aryl-allyl coupling reaction catalyzed by palladium complexes, arylmetals containing magnesium, zinc, and cadmium, in addition to those containing aluminum and zirconium, give the expected cross-coupled products. The yields with zinc or cadmium tend to be higher than those with aluminum or zirconium, whereas magnesium, in this respect, is inferior to aluminum or zirconium.[7] Related reactions of alkenylboranes[12] and alkenylmercury compounds[13] are also known, but their applicability to the selective synthesis of 1,4-dienes of terpenoid origin, such as α-farnesene, is unknown.

The synthesis of 1,4-dienes via cross coupling can, in principle, be achieved either by the reaction of allylmetals with alkenyl electrophiles or by the reaction of alkenylmetals with allyl electrophiles. The reaction of π-allylnickel derivatives with alkenyl halides[14] represents the former approach and can be highly regioselective. Stereo- and regio-defined alkenylmetals containing aluminum,[15] boron,[16] silicon,[17] and copper[18] have been reported to react with allylic electrophiles producing 1,4-dienes. With the possible exception of the organocopper reaction, the scope of these uncatalyzed reactions is practically limited to γ-unsubstituted allylic halides. Finally, the nickel-catalyzed reaction of Grignard reagents with allylic electrophiles[19] is also known, but the reaction is generally nonselective. Nor does it appear that the reaction has been applied to the synthesis of 1,4-dienes.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

α-Farnesene: 1,3,6,10-Dodecatetraene, 3,7,11-trimethyl- (8,9); (502-61-4)

Trimethylalane: Aluminum, trimethyl- (8,9); (75-24-1)

Dichlorobis(η^5-cyclopentadienyl)zirconium: Zirconium, dichloro-π-cyclopentadienyl- (8); Zirconium, dichlorobis(η^5-2,4-cyclopentadien-1-yl)- (9); (1291-32-3)

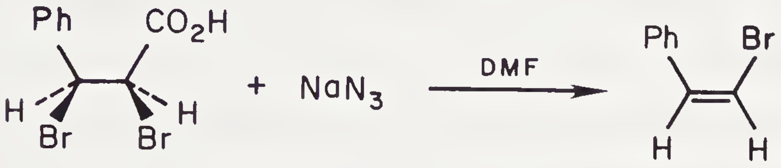
1-Buten-3-yne (8,9); (689-97-4)

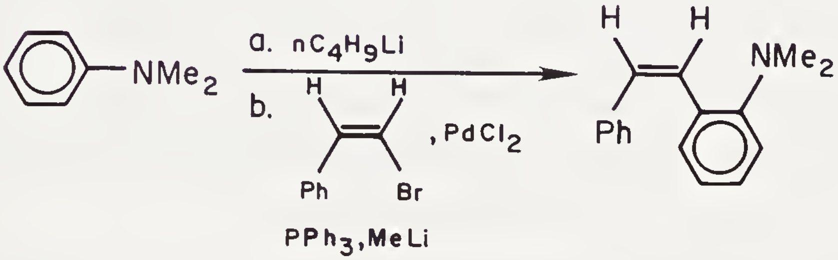
Geranyl chloride: (E)-2,6-Octadiene, 1-chloro-3,7-dimethyl- (8,9); (5389-87-7)

Tetrakis(triphenylphosphine)palladium: Palladium, tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

PALLADIUM-PHOSPHINE COMPLEX CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES: (Z)-β-[2-(N,N-DIMETHYLAMINO)PHENYL]STYRENE

(Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)-)





Submitted by Shun-Ichi Murahashi, Takeshi Naota, and Yoshio Tanigawa[1].

Checked by Joseph Fortunak and Ian Fleming.

1. Procedure

Caution! The reaction in Part A should be carried out in a well-ventilated hood because bromine is toxic.

A. (Z)-β-Bromostyrene. In a 1-L, round-bottomed flask equipped with a magnetic stirring bar are placed 30.8 g (0.100 mol) of *erythro*-α,β-dibromo-β-phenylpropionic acid (Note 1), 13.0 g (0.200 mol) of sodium azide (Note 2), and 500 mL of dry N,N-dimethylformamide (Note 3). The reaction mixture is stirred at room temperature for 8 hr, and poured into a mixture of 300 mL of ether and 300 mL of water. The organic layer is separated, washed with three 100 mL portions of water, dried over magnesium sulfate, and filtered. After evaporation of the filtrate with a rotary evaporator, the residual liquid is distilled under reduced pressure giving 13.5-13.9 g (74-76%) of (Z)-β-bromostyrene, bp 54-56°C (1.5 mm). (Note 4).

B. 2-(N,N-Dimethylamino)phenyllithium. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser connected to a nitrogen-inlet tube is capped with serum stoppers and flushed with nitrogen. The flask is charged with 18.2 g (0.150 mol) of N,N-dimethylaniline (Note 5) and 33.4 mL (0.050 mol) of a 1.50 M solution of n-butyllithium in hexane (Note 6). While a continuous positive nitrogen pressure is maintained, the solution is heated at reflux (in a 90-95°C bath) with stirring for 20 hr and then cooled to room temperature (Note 7).

C. (Z)-β-[2-(N,N-Dimethylamino)phenyl]styrene. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser connected to a nitrogen-inlet tube, and a 300-mL, pressure-equalizing dropping funnel is capped with serum stoppers. The flask is flushed with nitrogen and charged with 0.433 g (0.0025 mol) of palladium chloride (Note 8), 2.62 g (0.010 mol) of triphenylphosphine (Note 9), and 300 mL of benzene (Note 10). While a continuous positive nitrogen pressure is maintained, the mixture is stirred at gentle reflux for 30 min, and then 4.25 mL (0.0060 mol) of a 1.41 M solution of methyllithium in ether (Note 11) is added with a syringe. After an additional 10 min at reflux, 9.15 g (0.050 mol) of (Z)-β-bromostyrene prepared in Part A is added in one portion with a syringe, and the mixture is heated at reflux for 10 min. The solution of 2-(N,N-dimethylamino)phenyllithium prepared in Part B is transferred to the dropping funnel with a syringe, and diluted by adding 150 mL of benzene (Notes 10 and 12). The resulting solution is then added dropwise to the mixture with stirring at reflux over a period of 30 min (Note 13). After additional stirring for 10 min, the resulting red solution is cooled to room temperature with the help of an ice-bath, and quenched by adding 100 mL of saturated aqueous ammonium chloride. The organic layer is separated, washed successively with 100 mL of water and 100 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate and filtered. The solvent is evaporated with a rotary evaporator and the residue is distilled under reduced pressure to give a forerun (ca. 11 g) of excess N,N-dimethylaniline, bp 31-51°C (1 mm), followed by 7.4-7.5 g (66-67%) of (Z)-β-[2-(N,N-dimethylamino)phenyl]styrene, bp 90.0-92.0°C (0.035 mm), 82-84°C (0.01 mm), as a pale yellow liquid (Note 14).

2. Notes

1. *erythro*-α,β-Dibromo-β-phenylpropionic acid is prepared from trans-cinnamic acid (mp 133-134°C) (Nakarai Chemicals, Japan) by the method used for ethyl α,β-dibromo-β-phenylpropionate (Abbott T. W.; Althousen, D. *Org. Synth., Coll. Vol. 2* **1943**, 270) in 83% yield, mp 199-200°C. The checkers used benzene (400 mL per mol) in place of the carbon tetrachloride, because the mixture was then easier to stir and the reaction was more reproducible. The yield before purification was 89% (mp 174-191°C); the yield after recrystallization was 81% (mp 198-199°C). Crude material could be used without appreciable loss of yield.

2. Sodium azide from Wako Pure Chemical Ind., Japan, was used without purification.

3. N,N-Dimethylformamide is distilled over calcium hydride.

4. Gas chromatographic analysis of the distillate (10% PEG-20M on 60-80 mesh, Celite 545 AW, 1-m x 4-mm, column temperature 100-220°C, injection temperature 200°C) shows that the product is 100% isomerically pure. The spectral properties of the (Z)-β-bromostyrene are as follows: IR (neat) cm^{-1}: strong absorptions at 3095, 3040, 1620, 1500, 1450, 1333, 1032, 930, 920, 830, 770, and 700; ^1H NMR ($CHCl_3$) δ: 6.43 (doublet, 1 H, J=8, PhCH=C), 7.08 (doublet, 1 H, J=8, PhC=CHBr), 7.22-7.85 (multiplet, 5 H, aromatic). The checkers also purified the residual oil before distillation by filtration in 250 mL of pentane through three times its weight of silica gel (70-230 mesh) followed by evaportion. The yield before distillation was then reproducibly 84%, distillation was avoided, and the next step proceeded with undiminished yield.

5. N,N-Dimethylaniline from Nakarai Chemicals was dried over calcium hydride and freshly distilled. Three molar equivalents of N,N-dimethylaniline are used to achieve complete conversion of the n-butyllithium, because in the present particular case free n-butyllithium, if present, causes the isomerization of the (Z)-alkene to the (E)-isomer.

6. A solution of n-butyllithium in hexane was obtained from Aldrich Chemical Company, Inc. Before use the solution is titrated with a 1 M solution of 2-butanol in xylene according to the procedure of Watson and Eastham,[2] [see Gall, M.; House, H. O. *Org. Synth.* **1972**, *52*, 39] with 2,2'-biquinoline as indicator.

7. The resulting cloudy, yellowish orange solution should be used within 3-4 hr.

8. Palladium chloride from Inuisho Precious Metal Company, Japan, was used without purification.

9. Triphenylphosphine from Nakarai Chemicals, Japan, was used without purification.

10. Benzene is distilled over benzophenone ketyl and stored under a nitrogen atmosphere.

11. A solution of methyllithium in ether is prepared from lithium wire and methyl bromide according to the literature procedure,[3] and titrated by the same method as Note 6. The checkers used 1.1 M methyllithium from Aldrich.

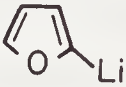
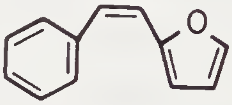
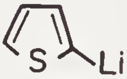
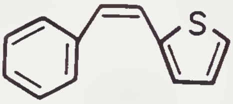
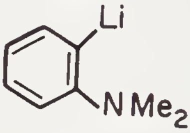
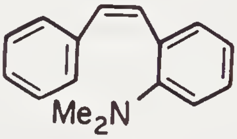
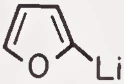
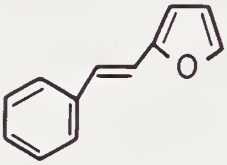
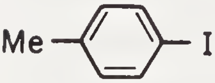
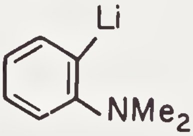
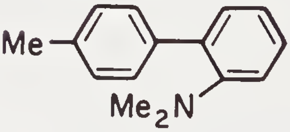
12. Without the dilution, (Z)-1,4-diphenyl-1-buten-3-yne is detected, apparently formed from the cross-coupling with phenylacetylide, derived from lithiation of β-bromostyrene, followed by E2cB elimination or Fritsch-Butlenberg-Wiechell type rearrangement.

13. Prolonged reaction time causes the isomerization of (Z)-β-[2-(N,N-dimethylamino)phenyl]styrene to the (E)-isomer.

14. Gas chromatographic analysis of the product (5% silicone SE 30 on 80-100 mesh Chromosorb W AB, 0.5-m x 4-mm, column temperature 100-250°C, injection temperature 180°C) shows that the product is at least 98% (Z)-isomer. The spectral properties of the (Z)-alkene are as follows; IR (neat) cm^{-1}: strong absorptions at 3070, 3025, 2950, 2870, 2835, 2780, 1600, 1490, 1450, 1320, 1190, 1160, 1140, 1100, 1050, 950, 780, 750, and 690; ^1H NMR (CCl_4) δ: 2.76 (singlet, 6 H, CH_3-N), 6.38 (doublet, 1 H, J=12.3, PhC=CH), 6.63 (doublet, 1 H, J=12.3, PhCH=C), 6.50-7.30 (multiplet, 9 H, aromatic).

Table I

PALLADIUM-CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES[a]

Halides	RLi	Products	Yield[b] (%)
(Z)-$C_6H_5CH{=}CHBr$	CH_3Li	(Z)-$C_6H_5CH{=}CHCH_3$	90
	$CH_3(CH_2)_3Li$	(Z)-$C_6H_5CH{=}CHC_4H_9$	62
			85
			94[c]
			87 (66-67)[d]
	C_6H_5SLi	(Z)-$C_6H_5CH{=}CHSC_6H_5$	95[c]
	C_2H_5SLi	(Z)-$C_6H_5CH{=}CHSC_2H_5$	93[c]
(E)-$C_6H_5CH{=}CHBr$	CH_3Li	(E)-$C_6H_5CH{=}CHCH_3$	88
			85
			(89)[d]

[a] The reaction was carried out on a 1.0-5.0 mmol scale. [b] Determined by gas chromatography. [c] Tetrakis(triphenylphosphine)palladium was used. [d] Isolated yield.

3. Discussion

The starting materials, (Z)-β-bromostyrene[4] and 2-(N,N-dimethylamino)-phenyllithium[5] have been prepared in satisfactory yields by known procedures after slight modifications. The azide procedure[4] gives higher stereospecificity than the earlier procedure using sodium bicarbonate.[6]

This procedure illustrates a general method for the preparation of alkenes from the palladium(0)-catalyzed reaction of vinyl halides with organolithium compounds,[7] which can be prepared by various methods, including direct regioselective lithiation of hydrocarbons.[8] The method is simple and has been used to prepare a variety of alkenes stereoselectively. Similar stoichiometric organocopper reactions sometimes proceed in a nonstereoselective manner[9] and in low yields.[10] Nickel catalysts can be used efficiently for the reaction of alkenyl halides with Grignard reagents but not with organolithium compounds.[11] Highly reactive zerovalent palladium catalyst can be directly generated in situ from $PdCl_2$-PPh_3-CH_3Li. Tetrakis(triphenylphosphine)-palladium can be used alternatively. Grignard reagents undergo the reaction as well with aryl halides. Organolithium compounds require the limited reaction condition under which the elimination of alkenyl halides producing lithium acetylides is slower than the cross-coupling reaction.[7] The choice of benzene as a solvent and the dilution of the solution satisfy the above conditions. The palladium-catalyzed alkylation of aryl halides with organolithium compounds proceeds efficiently without such difficulty.[7] Similar reactions with lithium thiolates gave the corresponding alkenyl sulfides.[7] Representative reactions of organolithium compounds are shown in Table I.

1. Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka, Japan.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(Z)-β-[2-(N,N-Dimethylamino)phenyl]styrene: Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)- (9); (70197-43-2)

(Z)-β-Bromostyrene: Styrene, β-bromo-, (Z)- (8); Benzene, (2-bromoethenyl)-, (Z)- (9); (588-73-8)

erythro-α,β-Dibromo-β-phenylpropionic acid: Hydrocinnamic acid, α,β-dibromo-, *erythro*- (8); Benzenepropanoic acid, α,β-dibromo-, (R^*,S^*)- (9); (31357-31-0)

trans-Cinnamic acid: Cinnamic acid, (E)- (8); 2-Propenoic acid, 3-phenyl-, (E)- (9); (140-10-3)

Sodium azide (8,9); (26628-22-8)

2-(N,N-Dimethylamino)phenyllithium: Lithium, [o-dimethylamino)phenyl]- (8); Lithium, [2-(dimethylamino)phenyl]- (9); (22608-37-3)

N,N-Dimethylaniline: Aniline, N,N-dimethyl- (8); Benzenamine, N,N-dimethyl- (9); (121-69-7)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

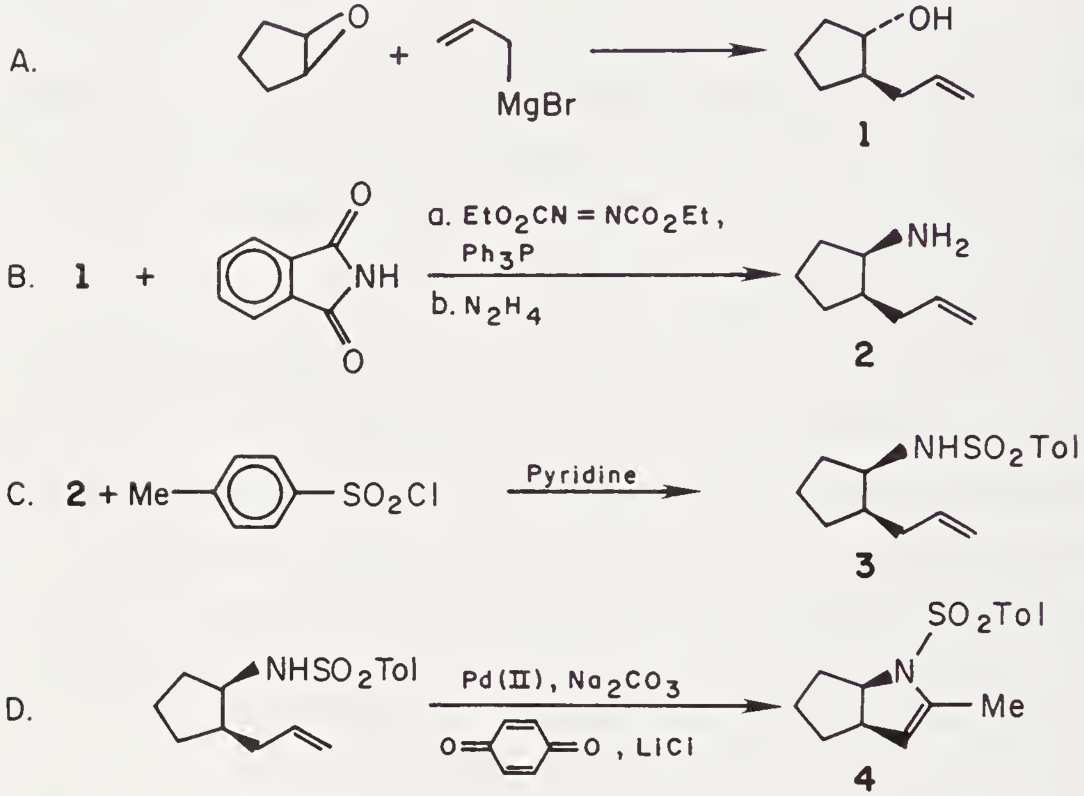
Palladium chloride (8,9); (7647-10-1)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Methyllithium: Lithium, methyl- (8,9); (917-54-4)

cis-N-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE

(Cyclopenta[b]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[4-methylphenyl)sulfonyl]-, cis-)



Submitted by Louis S. Hegedus, Michael S. Holden, and James M. McKearin[1]. Checked by Christoph Nübling and Ian Fleming.

1. Procedure

A. trans-2-(2-Propenyl)cyclopentanol. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser with a stopcock, and a 250-mL addition funnel is charged with 18.3 g (750 mmol) of magnesium turnings (Note 1). The system is evacuated and placed under argon, then 100 mL of ethyl ether (Note 2) is added to the system via cannula. The system is placed in an ice-water bath, and 2 mL of allyl bromide (Note 3) is added via syringe to the magnesium suspension to initiate Grignard formation. The addition funnel is charged with 45.5 g (375 mmol) of allyl bromide and 30 mL of ethyl ether. Another 100 mL of ethyl ether is added to the reaction flask. Stirring is begun, and the allyl bromide-ethyl ether mixture is added dropwise to the cooled reaction flask over a period of about 2 hr. After the addition is complete, the dark gray solution is stirred for several hours at ambient temperature (Note 4). Meanwhile, a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser with a stopcock, and a 60-mL addition funnel is evacuated and placed under argon. The Grignard solution is transferred, via cannula, into the flask, and 16.8 g (200 mmol) of cyclopentene oxide (Note 5) is placed in the addition funnel. While the solution is stirred, the epoxide is added dropwise to the Grignard reagent at a rate sufficient to maintain a mild reflux. After the solution is stirred for several hours or overnight, the flask containing the dark gray reaction mixture is placed in an ice-water bath, and excess Grignard reagent is hydrolyzed with 40 mL of a saturated aqueous ammonium chloride solution. The fine white precipitate is allowed to settle (Note 6), and the liquid is decanted into a 500-mL separatory funnel. The precipitate is washed with ethyl ether (4 x 50 mL) (Note 7), and all the ethyl ether solutions are combined, washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL), then with saturated aqueous sodium chloride (2 x 20 mL). The aqueous layers are combined and washed with ethyl ether (2 x 20 mL). The ether layers are combined and dried over anhydrous potassium carbonate. The desiccant is removed by gravity filtration, and the solvent removed under reduced pressure to give 24.1-26.4 g (96-105%) of a yellow oil. Distillation (43°C, 0.250 mm) yields 1 (19.8-23.0 g. 78-91%) as a clear, colorless oil (Note 8).

B. cis-2-(2-Propenyl)cyclopentylamine. A 1000-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two addition funnels, and a stopcock is charged with 41.5 g (158 mmol) of triphenylphosphine (Note 9) and 23.3 g (158 mmol) of phthalimide (Note 10). The system is evacuated and placed under argon. To one addition funnel, 20.0 g (158 mmol) of trans-2-(2-propenyl)cyclopentanol is added; 27.5 g (158 mmol) of diethyl azodicarboxylate (Note 11) is added to the other. Tetrahydrofuran, 500 mL, (Note 12) is added to the flask via cannula, and stirring is begun. The substrate and diethyl azodicarboxylate are simultaneously added dropwise, slowly over about 30 min (Note 13), with stirring; the solution turns clear and yellow (Note 14). The reaction is permitted to proceed for 2 days at room temperature; the solution is then transferred to a 1000-ml, one-necked, round-bottomed flask, and the solvent is removed under reduced pressure, to leave a yellow-white semi-solid. A magnetic stirring bar is added to the flask and the semi-solid is taken up in 250 mL of reagent-grade methyl alcohol. To this, 10.1 g (316 mmol) of hydrazine (Note 15) is added. A reflux condenser is attached to the flask, stirring is begun, and the system is brought to reflux (Note 16). A large amount of clumpy white solid forms in a yellow-to-orange solution. After 4 hr at reflux, the solution is allowed to cool to room temperature; a mixture of 20 mL of hydrochloric acid (Note 17) and 65 mL of methyl alcohol is added, and the system is refluxed overnight. The resulting reaction mixture is filtered to remove the precipitate, and the solvent is removed under reduced pressure to yield a white-to-pink solid, which is taken up in 800 mL of water and 28 mL of hydrochloric acid. The solution is filtered, and the solid washed with water (2 x 200 mL) and hydrochloric acid (20 mL). The liquids are combined, placed in a 2000-mL separatory funnel, and washed with chloroform (3 x 250 mL), and ethyl ether (1 x 250 mL). The aqueous layer is transferred to a 2000-mL Erlenmeyer flask, and cooled in an ice-water bath. A saturated aqueous sodium hydroxide solution is used to make the solution basic, to approximately pH 14, whereupon the solution turns dark olive green. The basic solution is extracted with ethyl ether (10 x 250 mL), or by continuous extraction overnight and the combined organic layers are dried over a mixture of anhydrous sodium sulfate and anhydrous potassium carbonate. Filtration and solvent removal at atmospheric pressure yields a green-yellow oil. Distillation (52-58°C, 8-11 mm) gives 2 (11.8-12.5 g, 60-63%) as a clear, colorless oil (Note 18).

C. cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine. A 100-mL, one-necked, round-bottomed flask equipped with a sidearm, a magnetic stirring bar, stopcock, and a serum cap on the sidearm, is charged with 8.00 g (64 mmol) of cis-2-(2-propenyl)cyclopentylamine. The system is evacuated and placed under argon. Via cannula, 50 mL of pyridine (Note 19) is added. The flask is cooled in an ice-water bath, the stopcock removed, 12.58 g (66 mmol) of p-toluenesulfonyl chloride (Note 20) is added to the reaction mixture, and the stopcock replaced. The reaction mixture immediately turns orange; it is allowed to stir at 0°C overnight, during which time the reaction mixture turns deep purple. The reaction mixture is then poured into a separatory funnel, 60 mL of distilled technical grade ethyl acetate is added, and the solution is washed with 100-mL portions of 1:1 2 N HCl: saturated aqueous sodium chloride until the washings are acidic. The organic layer is washed with saturated aqueous sodium chloride (2 x 60 mL), and dried over anhydrous magnesium sulfate. Gravity filtration and solvent removal under reduced pressure yield a dark red-brown solid. This is purified by recrystallization from 250 mL of ethyl alcohol/water (4:1); crystallization is completed in the refrigerator to give **3** (12.7-13.9 g, 71-78%) as off-white plates, mp 109-110°C (Note 21).

D. cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene. A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser is charged with 5.159 g (18.49 mmol) of cis-1-N-tosyl-2-(2-propenyl)cyclopentylamine, 1.998 g (18.49 mmol) of p-benzoquinone (Note 22), 0.096 g (0.370 mmol, 2 mole-%) of $PdCl_2(CH_3CN)_2$ (Note 23), 3.920 g (92.46 mmol, 500 mole-%) of lithium chloride (Note 24), and 1.960 g (18.49 mmol) of sodium carbonate (Note 25). Tetrahydrofuran (100 mL) (Note 12) is added and stirring is begun. The yellow-orange solution is heated at reflux until thin-layer chromatography (3:1 hexane:ethyl acetate, SiO_2) shows that no starting material remains (about 3-4 hr); it is then poured into a 500-mL separatory funnel and 100 mL of ethyl acetate is added. This is washed with 100-mL portions of 1:1 saturated aqueous sodium chloride: sodium hydroxide (1%) until the aqueous layer is clear; then the yellow-green organic layer is washed with saturated aqueous sodium chloride (2 x 50 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered by gravity, passed through a short column (approximately 5 cm) of neutral alumina, and the column is washed with 100 mL of ethyl acetate. The combined solvents are removed under reduced pressure to give 4.9-5.1 g (94-99%) of a tan solid. The product is recrystallized from 100 mL of methyl alcohol/water (4:1) to yield **4** (3.9-4.45 g, 76-87%) as white needles, mp 91-92°C (Notes 26 and 27).

2. Notes

1. Magnesium turnings, purified for Grignard reactions, are purchased from J. T. Baker Chemical Company, and used without further purification.

2. Ethyl ether is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.

3. Allyl bromide, purchased from Aldrich Chemical Company, Inc., is distilled and stored in a brown bottle away from light.

4. Successful reactions have been run with this induction period lasting from 1 hr to overnight.

5. Cyclopentene oxide is purchased from Arapahoe Chemicals, Boulder, CO, and used without purification. The checkers bought cyclopentene oxide from Lancaster Synthesis.

6. The fine precipitate may take several hours to settle. Filtration is often ineffective, but settling can be speeded up by centrifuging.

7. Since the efficiency of this washing is dependent upon the degree of settling, the checkers recommend that washing with 50-mL batches of ether be continued until the smell of the alcohol is no longer detectable on a sample of the dry salts.

8. The spectral properties are as follows: ^1H NMR ($CDCl_3$) δ: 1.0-2.4 (m, 9 H); 3.0-3.3 (br s, 1 H, O-H); 3.7-4.1 (m, 1 H, CH-O); 4.8-5.3 (m, 2 H, $=CH_2$); 5.5-6.2 (m, 1 H, -CH=).

9. Anhydrous triphenylphosphine is purchased from Sigma Chemical Company, and is used without further purification.

10. Phthalimide, 98%, is purchased from Aldrich Chemical Company, Inc., and is used without further purification.

11. Diethyl azodicarboxylate is purchased from Aldrich Chemical Company, Inc., and is used without further purification.

12. Tetrahydrofuran is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.

13. Too rapid a rate of addition may cause the solution to boil.

14. The solution does not become homogeneous until it is warmed by the heat of the reaction.

15. Anhydrous hydrazine, 97+%, is purchased from Matheson, Coleman and Bell, Norwood, OH 45212, and is used without further purification.

16. Because of the dangerous nature of hydrazine, a safety shield should always be in place during this reaction.

17. A.C.S. Reagent hydrochloric acid is purchased from Fisher Scientific Company, and used without further purification.

18. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.8 (s, 2 H, NH_2); 1.3-2.4 (m, 9 H, CH_2, CH); 3.1-3.4 (m, 1 H, HC-N); 4.8-5.2 (m, 2 H, =CH_2); 5.4-6.1 (m, 1 H, HC=).

19. Pyridine is distilled from CaH_2 and stored over CaH_2 under argon.

20. p-Toluenesulfonyl chloride is purchased from J. T. Baker Chemical Company, and purified by dissolving 20 g in 50 mL of chloroform, adding 250 mL of hexane, filtering, and solvent removal under reduced pressure.[2]

21. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.0-2.3 (m, 9 H, CH_2, CH); 2.41 (s, 3 H, CH_3); 3.4-3.8 (m, 1 H, CHN); 4.7-5.1 (m, 3 H, =CH_2, NH); 5.2-6.1 (m, 1 H, =CH); 7.25 (d, 2 H, J = 8, ArH); 7.8 (d, 2 H, J = 8, ArH).

22. p-Benzoquinone, 98+%, is purchased from the Aldrich Chemical Company, Inc., sublimed at 60°C/15 mm, and stored under argon. The checkers used it as supplied.

23. Palladium(II) chloride-acetonitrile complex is formed by placing 8.00 g of $PdCl_2$ in 200 mL of acetonitrile and stirring for 2 days or refluxing for 3 hr. The complex (11.43 g, 97.8%) is collected by filtration, washed, and dried.

24. Lithium chloride is purchased from Fisher Scientific Company and used without further purification.

25. Sodium carbonate is purchased from Aldrich Chemical Company, Inc., and used without further purification.

26. The spectral properties are as follows: ^1H NMR ($CDCl_3$) δ: 1.40-2.00 (m, 6 H, CH_2); 2.10 (m, 3 H, CH_3C=); 2.40 (s, 3 H, $ArCH_3$); 2.80-3.20 (m, 1 H, 4.20-4.50 (m, 1 H, CHN); 4.70 (m, 1 H, CH=); 7.30 (d, 2 H, J = 8, ArH); 7.70 (d, 2 H, J = 8, ArH).

27. The checkers also carried out the entire sequence on three times the scale with slightly better yields.

3. Discussion

Synthesis of the title compound is representative of a number of syntheses of nonaromatic nitrogen heterocycles via Pd(II)-catalyzed amination of olefins.[3] These tosylated enamines are not readily available by standard synthetic methods, and show potential for further functionalization of the heterocycle.[4] The saturated amine can be synthesized from the title compound by hydrogenation of the double bond followed by photolytic deprotection.[3]

In terms of cost, the effectiveness of the catalytic cycle in the ring closure makes this process economical in palladium. The first three steps in the reaction sequence -- ring opening of an epoxide by a Grignard reagent,[5] converison of an alcohol to an amine with inversion,[6] and sulfonamide formation from the amine[7] -- are all standard synthetic processes.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene: Cyclopenta[b]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[(4-methylphenyl)sulfonyl]-, cis- (11); (81097-07-6)

trans-2-(2-Propenyl)cyclopentanol: Cyclopentanol, 2-(2-propenyl)-, trans- (10); (74743-89-8)

Magnesium (8,9); (7439-95-4)

Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

Cyclopentene oxide: 6-Oxabicyclo[3.1.0]hexane (8,9); (285-67-6)

cis-2-(2-Propenyl)cyclopentylamine: Cyclopentanamine, 2-(2-propenyl)-, cis- (11); (81097-02-1)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Phthalimide (8); 1 H-Isoindole-1,3(2H)-dione (9); (85-41-6)

Diethyl azodicarboxylate: Formic acid, azodi-, diethyl ester (8): Diazenedicarboxylic acid, diethyl ester (9); (1972-28-7)

Hydrazine (8,9); (302-01-2)

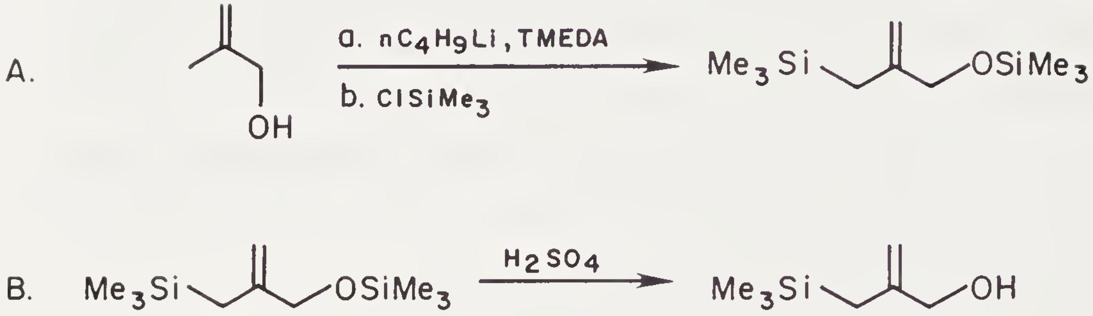
cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine: Benzenesulfonamide, 4-methyl-N-[2-(2-propenyl)cyclopentyl]-, cis- (11); (81097-06-5)

p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

p-Benzoquinone: Benzoquinone (8); 2,5-Cyclohexadiene-1,4-dione (9); (106-51-4)

Palladium(II) chloride: Palladium chloride (8,9); (7647-10-1)

SILYLATION OF 2-METHYL-2-PROPEN-1-OL DIANION: 2-(HYDROXYMETHYL)ALLYLTRIMETHYLSILANE



Submitted by Barry M. Trost, Dominic M. T. Chan, and Thomas N. Nanninga[1].

Checked by Paul R. Jenkins and Ian Fleming.

1. Procedure

Caution! Part A should be carried out in an efficient hood, since the reagents are noxious.

A. 2-(Trimethylsiloxymethyl)allyltrimethylsilane. An oven-dried (Note 1) 2-L, three-necked, round-bottomed flask is equipped with an air-tight mechanical stirrer (Note 2), a 500-mL pressure-equalizing dropping funnel (Note 3), and a reflux condenser. The top of the condenser is connected to a three-way stopcock with one branch connected to a nitrogen source and the other to a variable pressure oil pump with a dry-ice trap (Note 4). The apparatus is flamed dry under a steady stream of nitrogen. The flask is charged with 836 mL (1.07 mol) of a 1.28 M solution of n-butyllithium in hexane (Note 5). The bulk of the hexane is removed at reduced pressure with stirring until a thick oil is obtained (Note 6). The system is carefully recharged with nitrogen. The n-butyllithium is then cooled in an ice bath and 500 mL of anhydrous ether is added (Note 7), followed by 160 mL of tetramethylethylenediamine (Note 8). The mixture is stirred for a few minutes and 34 mL, 29.14 g (0.404 mol) of 2-methyl-2-propen-1-ol (Note 9) is added dropwise via a syringe over 22 min (Note 10). An immediate, vigorous reaction occurs and the lithium alkoxide precipitates as a white solid. Approximately 350 mL of tetrahydrofuran (Note 11) is added and the resultant slightly cloudy yellow solution is allowed to warm to room temperature over ca. 4 hr (Note 12). The reaction is stirred for 39 hr (Note 13) at which time the dianion separates as a dark red gummy material from the deep orange solution. The mixture is cooled to ca. -30°C (Note 14) and 230 mL (1.81 mol) of chlorotrimethylsilane (Note 15) is added all at once over ca. 20 sec. The reaction turns milky white (Note 16). After 5 min, the dry ice bath is removed and the mixture is stirred for a further 15 min at room temperature. The reaction mixture is added in two portions with swirling to 1.5 L of ether in two 2-L conical flasks, after which 1 L of saturated aqueous sodium bicarbonate is added very carefully to destroy excess chlorotrimethylsilane (Note 17). The two layers are separated and the aqueous phase is extracted with a further 1.5 L of ether. The combined organic layer is then washed with 1 L of water, two 1-L portions of saturated aqueous copper sulfate solution and 400 mL of water. The solution is dried over anhydrous potassium carbonate and the solvent is removed by atmospheric distillation (Note 18). Careful distillation of the residual oil through a 27-cm Vigreux column at reduced pressure gives a forerun of 4.25 g, bp 29-57°C (4 mm), and 45.8 g (52%) of 2-(trimethylsiloxy)allyltrimethylsilane as a colorless liquid, bp 57-59°C (4 mm) (Note 19).

B. 2-(Hydroxymethyl)allyltrimethylsilane. A 500-mL round-bottomed flask equipped with a magnetic stirring bar is charged with 21.10 g (0.0975 mol) of 2-(trimethylsiloxymethyl)allyltrimethylsilane in 170 mL of tetrahydrofuran (Note 11) and 44 mL of ca. 1 N aqueous sulfuric acid (Note 20). The resultant two-phase mixture is then stirred vigorously for 1.5 hr at room temperature. Solid anhydrous potassium carbonate is added carefully until bubbling subsides. The layers are separated and the aqueous layer is extracted with 100 mL of ether. The combined organic layers are dried over anhydrous potassium carbonate and distilled at atmospheric pressure to remove the solvents (Note 18). The remaining liquid is distilled at reduced pressure to give a forerun, 0.4 g, bp 22-54°C (4 mm), and 10.95 g (78%) of 2-(hydroxymethyl)-allyltrimethylsilane as a colorless liquid, bp 54-56°C (2 mm) (Note 21).

2. Notes

1. All glassware was dried in an oven at over 100°C overnight.

2. The use of a magnetic stirrer is not advisable since the formation of the gum-like dianion prevents efficient stirring. A mechanical stirrer with a ground-glass shaft bearing lubricated with mineral oil is recommended.

3. The funnel is capped with a rubber septum. For ease of operation, volume markings, corresponding to the amounts of reagents to be added, are put on the addition funnel.

4. The function of the trap is to condense the hexane from the n-butyllithium solution. The checkers used a 1-L three-necked flask fitted with a short delivery tube (a quick fit air bleed tube was used), stopper, and rubber tubing connection. The submitters used a water aspirator and a 1-L filter flask with a drying tower between.

5. n-Butyllithium in hexane was purchased by the checkers from Pfizer Chemicals Ltd., UK, and manufactured by the Lithium Corporation of America. It was titrated using the double titration method with dibromoethane and transferred to the addition funnel using a cannula. The submitters used a 1.58 M solution from the Foote Mineral Company; they found that the yield of product was reduced to ca. 42% when only two equivalents of the lithium reagent were used.

6. One should try to remove as much hexane as possible from the n-butyllithium solution (i.e. greater than 90%) because the purity of the product depends on the polarity of the reaction medium. A warm water bath was used to facilitate solvent removal. The checkers used a variable pressure oil pump with the vacuum adjusted to ca. 10-20 mm.

7. Ether was distilled from sodium ketyl of benzophenone. The dissolution of n-butyllithium in ether was slightly exothermic.

8. Tetramethylethylenediamine was obtained from Aldrich Chemical Company and distilled from calcium hydride before use.

9. 2-Methyl-2-propen-1-ol, purchased from Aldrich Chemical Company, was distilled from anhydrous potassium carbonate. It was added directly to the n-butyllithium solution using a long needle. The checkers quickly replaced the pressure-equalizing dropping funnel with a serum cap to carry out this addition. The funnel was fitted to a small dry flask to prevent the introduction of moisture during the addition period and replaced on the reaction flask immediately afterwards.

10. The reaction of the alcohol with n-butyllithium is quite vigorous with evolution of butane.

11. Tetrahydrofuran was distilled from sodium ketyl of benzophenone.

12. The checkers renewed the ice bath when additions were complete and allowed the flask to remain in the ice bath without addition of fresh ice.

13. Dianion formation appears to be essentially complete within 24 hr. However, a reaction time of 36 hr is recommended by the submitters to ensure complete reaction.

14. An extremely violent reaction is observed if the dianion is quenched above 0°C, with ether boiling off at an uncontrollable rate. The submitters observed that if the chlorotrimethylsilane addition is performed at a lower temperature, the reaction temperature will remain below that of the boiling point of ether. A dry-ice bath made up of 80:20 (v/v) ethanol-water was used; the checkers measured a bath temperature of -55°C and kept the reaction in the bath for 15 min before adding chlorotrimethylsilane.

15. Chlorotrimethylsilane was distilled from tributylamine before use. Both of these reagents were obtained from the Aldrich Chemical Company.

16. The submitters observed the appearance of a brown color at this point. The checkers obtained a brown color only after the reaction mixture was added to ether. In a run at half scale the reaction mixture remained milky white for 35 min and turned brown only when ether (500 mL) was added to it.

17. The submitters observed more precipitate on dilution with ether and recommended that the aqueous workup be performed in a hood.

18. The submitters distilled most of the solvent using a bath temperature increasing up to 100°C. The checkers used a rotary evaporator with a hot water bath.

19. A variable pressure oil pump was used in this distillation. Approximately 10 g of a volatile component, consisting mostly of hexamethyldisiloxane, was obtained at room temperature (15 mm) before the forerun. The forerun contained the desired product and mineral oil from the n-butyllithium solution. The pot residue was about 5 g. The submitters find the disilyl compound thus obtained is contaminated with a trace amount of mineral oil and 4-6% of a vinylsilane, probably 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene. This impurity becomes quite significant if the reaction medium is less polar than the one described (e.g., too much hexane from n-butyllithium is allowed to remain behind). The spectral properties of the desired product determined by the checkers are as follows: IR (neat) cm^{-1}: 2955, 1643, 1636, 1250, 1085, 885-830; ^1H NMR (chloroform-d, 90 MHz) δ: 0.03 (s, 9 H, $CH_2Si(CH_3)_3$), 0.14 (s, 9 H, $OSi(CH_3)_3$), 1.50 (broad s, 2 H, CH_2-$Si(CH_3)_3$), 3.93 (broad s, 2 H, CH_2-$OSi(CH_3)_3$), 4.62 (m, 1 H, vinyl H), 4.92 (m, 1 H, vinyl H).

The checkers observed small NMR peaks assigned to mineral oil at δ 0.9 and 1.28 and peaks assigned to 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene at δ 1.87 and 4.1. When the reaction was carried out at half scale the quantity of the latter impurity was not measurable from the NMR integral; however, a run at full scale gave about 10% of the impurity as estimated from the NMR integral. The product from the run at half scale had bp 56-57°C (2 mm), submitters bp 65°C (5.5 mm).

20. The acid solution was prepared by adding 13.5 mL of concentrated sulfuric acid to 500 mL of distilled water.

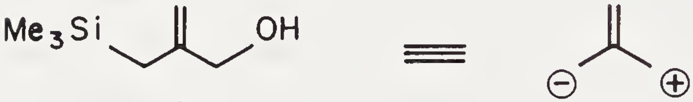
21. A variable pressure pump is used for the distillation. The forerun consisted of mineral oil contaminant and product. The allylic alcohol is not very stable at room temperature but can be kept indefinitely in the refrig-

erator at 0 to -6°C. The spectral properties of the alcohol were determined by the checkers as follows: IR (neat) cm^{-1}: 3600-3100, 2950, 1643, 1637, 1247, 1050, 885-830; ^1H NMR (chloroform-d), 90 MHz) δ: 0.02 (s, 9 H, $CH_2Si(CH_3)_3$), 1.51 (s, 2 H, CH_2-$Si(CH_3)_3$), 2.16 (broad s, 1 H, OH), 3.92 (broad s, 2 H, CH_2-OH), 4.62 (m, 1 H, vinyl H), 4.98 (m, 1 H, vinyl H).

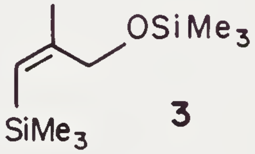
The checkers observed small NMR peaks assigned to mineral oil at δ 0.82 and 1.51 and peaks assigned to 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene at δ 0.10, 1.87 and 4.1. When the reaction was carried out at half scale the quantity of the latter impurity was reduced; the product from the run at half scale had bp 54-55°C (3 mm), submitters bp 53-54°C (1.6 mm).

3. Discussion

Compound **1**, 2-(hydroxymethyl)allyltrimethylsilane, represents a conjunctive reagent which can be considered as the equivalent of zwitterion **2**, possessing a nucleophilic allyl anion synthon and an electrophilic allyl cation synthon in the same molecule. It has been employed in a three-carbon condensative ring expansion reaction,[2] a [3+2] annulation with cyclic enones,[3,4] and the total synthesis of coriolin.[5] Acetylation of the allylic alcohol gives 2-(acetoxymethyl)allyltrimethylsilane, which undergoes palladium(0) catalyzed annulation with electron deficient olefins to produce



1 **2**



3

methylenecyclopentanes via the trimethylenemethane-palladium complex.[4] This cycloaddition has served as a key step in synthetic approaches directed toward natural products such as brefeldin A[6] and albene.[7]

The present procedure provides a convenient two-step route to 2-(hydroxymethyl)allyltrimethylsilane using relatively inexpensive reagents. Other approaches require more steps and expensive chloromethyltrimethylsilane.[3,8]

Dianion formation from 2-methyl-2-propen-1-ol seems to be highly dependent on reaction conditions. Silylation of the dianion generated using a previously reported method[9] was unsuccessful in our hands. The procedure described here for the metalation of the allylic alcohol is a modification of the one reported for formation of the dianion of 3-methyl-3-buten-1-ol.[10] The critical variant appears to be the polarity of the reaction medium. In solvents such as ether and hexane, substantial amounts (15-50%) of the vinylsilane **3** are observed. Very poor yields of the desired product were obtained in dimethoxyethane and hexamethylphosphoric triamide, presumably because of the decomposition of these solvents under these conditions. Empirically, the optimal solvent seems to be a mixture of ether and tetrahydrofuran in a ratio (v/v) varying from 1.4 to 2.2; in this case **3** becomes a very minor component.

A similar procedure has been employed to silylate the dianion of 3-methyl-3-buten-2-ol (67% yield).[11] In systems where such internal activation is not possible (e.g. 2-methyl-2-cyclohexen-1-ol), dianion formation can be performed in hexane to give a 75% yield of the corresponding disilyl compound.[12]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

n-Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Tetramethylethylenediamine: Ethylenediamine, N,N,N',N'-tetramethyl- (8); 1,2-Ethanediamine, N,N,N',N'-tetramethyl- (9); (110-18-9)

2-Methyl-2-propen-1-ol: 2-Propen-1-ol, 2-methyl- (8,9); (513-42-8)

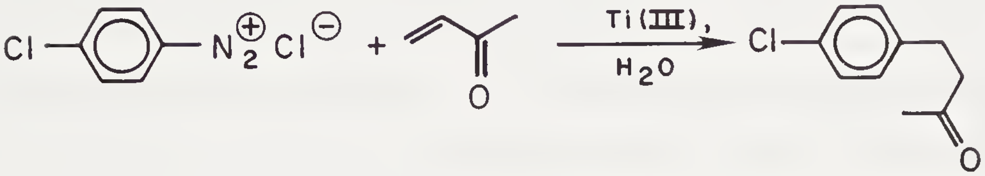
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

2-(Acetoxymethyl)allyltrimethylsilane: 2-Propen-1-ol, 2-[(trimethylsilyl)-methyl]-, acetate (10); (72047-94-0)

REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS:

4-(4-CHLOROPHENYL)BUTAN-2-ONE

(2-Butanone, 4-(4-chlorophenyl)-)



Submitted by Attilio Citterio.

Checked by Robert Haessig, Leo Widler, and Dieter Seebach.

1. Procedure

Caution! Like all vinyl monomers, 3-buten-2-one is toxic and the preparation should be carried out in a well-ventilated hood.

A 500-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a gas inlet, an externally cooled, pressure-equalizing dropping funnel (Note 1), and a gas bubbler is charged with 15% aqueous titanium trichloride (92 mL, 0.109 mol) (Note 2). N,N-Dimethylformamide (Note 3) (70 mL) is added during 45 min with stirring and cooling (ice-bath; 0-5°C) while nitrogen is bubbled through the solution. Freshly distilled 3-buten-2-one (5.7 mL, 0.066 mol) is added at 0-5°C by syringe. The nitrogen flow is stopped, and 4-chlorobenzenediazonium chloride solution (0.044 mol) (Note 4) is added dropwise at 0-5°C from the dropping funnel. After 2-3 min, nitrogen evolution commences, and the rate of addition is adjusted so that 1-2 bubbles/sec are vented through the bubbler. Nitrogen evolution continues for 20 min after the addition is complete (1.5 hr). The ice-bath is removed and the solution stirred for 1 hr at room temperature. Ether, 50 mL, is added with stirring, and the organic phase is separated. The aqueous phase is extracted with ether (3 x 50 mL) and the combined organic extracts are washed with 3% aqueous Na_2CO_3 (2 x 30 mL) and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is distilled to give 5.2-6.0 g (65-75% yield) of 4-(4-chlorophenyl)butan-2-one as a pale-yellow liquid, bp 90-91°C (0.5 mm) (Note 5).

2. Notes

1. The checkers used a dropping funnel with temperature-control jacket (Normag N 8055, Otto Fritz GmbH, Normschliff-Aufbaugeräte (Normag), D-6238 Hofheim am Taunus).

2. The 15% titanium trichloride solution was purchased from Carlo Erba Chemicals or from Merck & Company, Inc., but can also be prepared by dissolving metallic titanium in 20% aqueous hydrochloric acid[2] or by dissolving solid titanium trichloride in 1 M aqueous hydrochloric acid. Titanium(III) sulfate (from BDH Chemicals Ltd.) can also be used. All titanium(III) solutions were titrated with aqueous cerium(IV) sulfate prior to use.

3. N,N-Dimethylformamide from Carlo Erba Chemicals, from Fluka AG, or from Merck & Company, Inc. was used as received. Other solvents (for example, acetone, acetic acid, acetonitrile) can also be used.

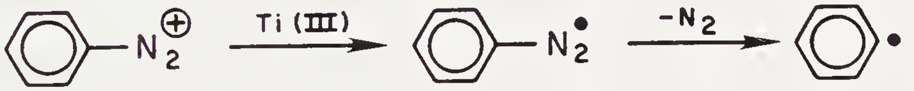
4. The 4-chlorobenzenediazonium chloride solution is prepared as follows: finely powdered 4-chloroaniline (5.65 g, 0.044 mol) is suspended in 18 mL of 24% aqueous hydrochloric acid and cooled to 0°C. Sodium nitrite (3.2 g, 0.046 mol) in water (7 mL) is added dropwise during 45 min at 0-5°C to give a pale yellow solution of the diazonium salt.

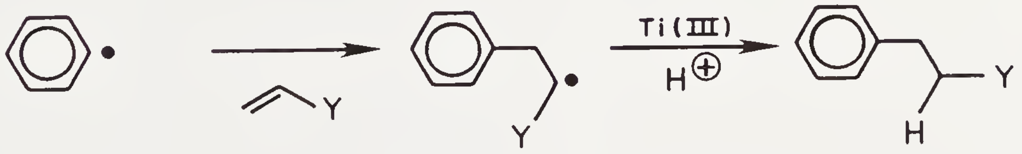
5. The physical properties of the product are as follows: n_D^{25} 1.5251; IR (liquid film) cm^{-1}: 1715; ^{1}H NMR (CDCl$_3$) δ: 2.0 (s, 3 H), 2.6-2.8 (m, 4 H), 6.8-7.3 (m, 4 H); mass spectrum m/e: 182 (M); semicarbazone, mp 165°C (164-165.5°C[4]). GLC analysis (glass capillary column, 20 m, pluronic L-64, program: 120-200°C at 5°C/min): >99% pure.

3. Discussion

This synthesis is only one example of a wide range of reactions which involve aryl (or alkyl) radical addition to electron-deficient double bonds resulting in reduction.[3,5,6] The corresponding oxidative reaction using aryl radicals is the well known Meerwein reaction,[7] which uses copper(II) salts.

General arylation reactions are summarized by the following equations and some specific examples are presented in Table I.





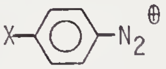
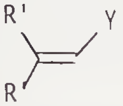
Homolytic cleavage of diazonium salts to produce aryl radicals is induced by titanium(III) salt, which is also effective in reducing the α-carbonylalkyl radical adduct to olefins, telomerization of methyl vinyl ketone, and dimerization of the adduct radicals. The reaction can be used with other electron-deficient olefins, but telomerization or dimerization are important side reactions.

Other limitations of the reaction are related to the regioselectivity of the aryl radical addition to double bond, which is mainly determined by steric and radical delocalization effects.[8] Thus, methyl vinyl ketone gives the best results, and lower yields are observed when bulky substituents are present in the β-position of the alkene. However, the method represents complete positional selectivity because only the β-adduct radicals give reductive arylation products whereas the α-adduct radicals add to diazonium salts, because of the different nucleophilic character of the alkyl radical adduct.[8,9]

The product described here, 4-(4-chlorophenyl)butan-2-one, was previously prepared in the following ways: a) by reduction of the corresponding benzalacetone,[10] b) by catalyzed decarbonylation of 4-chlorophenylacetaldehyde by $HFe(CO)_4$ in the presence of 2,4-pentanedione,[11] c) by reaction of 4-chlorobenzyl chloride with 2,4-pentanedione under basic catalysis (K_2CO_3 in EtOH),[4] d) by reaction of 4-chlorobenzyl chloride with ethyl 3-oxobutanoate under basic catalysis (LiOH),[12] and e) by reaction of 3-(4-chlorophenyl)-propanoic acid with methyllithium.[13]

TABLE I

REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS BY ARENEDIAZONIUM SALTS INDUCED BY TITANIUM(III) SALTS

				yield[a]
X	R	R'	Y	(%)
4-OCH_3	H	H	$COCH_3$	65
H	H	H	$COCH_3$	75
4-Br	H	H	$COCH_3$	68
4-$COCH_3$	H	H	$COCH_3$	72
4-Cl	H	H	CHO	63
4-Cl	CH_3	H	$COCH_3$	44
4-Cl	$CH(CH_3)_2$	H	$COCH_3$	28
4-Cl	$C(CH_3)_3$	H	$COCH_3$	14
4-Cl	CH_3	CH_3	$COCH_3$	12
4-Cl	Ph	H	$COCH_3$	18
4-Cl	H	H	CN	25[b]
4-Cl	H	H	COOH	33[b]
4-Cl	H	H	COOEt	32[b]

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[a] From the diazonium salt. [b] Telomers are formed; the reactions are carried out with twice the amount of titanium(III) salt.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

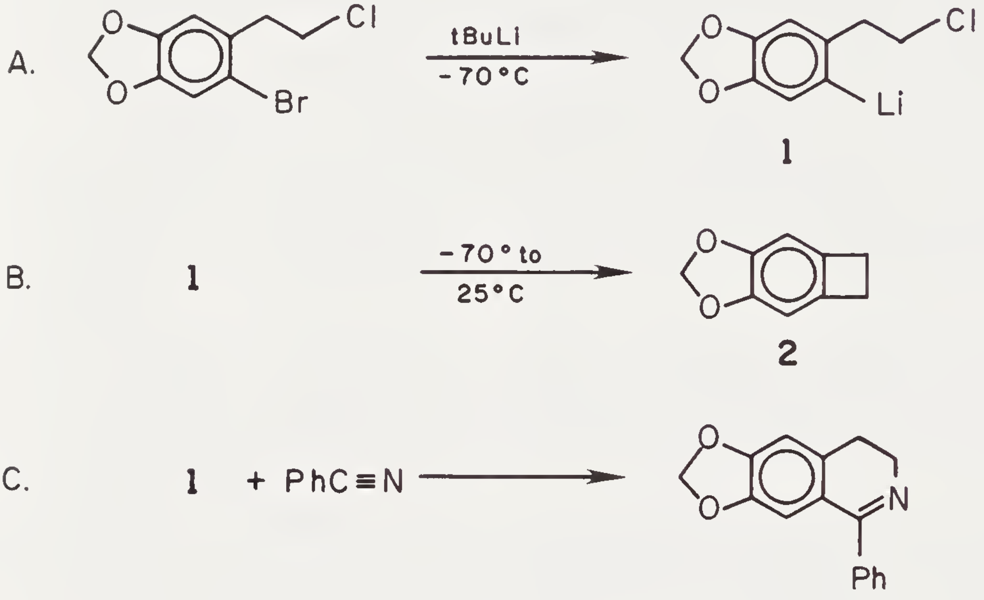
4-(4-Chlorophenyl)butan-2-one: 2-Butanone, 4-(p-chlorophenyl)- (8); 2-Butanone, 4-(4-chlorophenyl)- (9); (3506-75-0)

3-Buten-2-one (8,9); (78-94-4)

Titanium trichloride: Titanium chloride (8,9); (7705-07-9)

SELECTIVE HALOGEN-LITHIUM EXCHANGE REACTIONS OF 2-(2'-HALOPHENYL)ETHYL HALIDES: SYNTHESIS OF 4,5-METHYLENEDIOXYBENZOCYCLOBUTENE AND 1-PHENYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE

(Cyclobuta[*f*]-1,3-benzodioxole, 5,6-dihydro- and
1,3-dioxolo[4,5-*g*]isoquinoline, 7,8-dihydro-5-phenyl-)



Submitted by Dennis J. Jakiela, Paul Helquist,[1] and Lawrence D. Jones[2].

Checked by Neville D. Emslie and Ian Fleming.

1. Procedure

A. 2-(2'-Lithio-4',5'-methylenedioxyphenyl)ethyl chloride. A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel (Note 1), low temperature thermometer, and a three-way stopcock having a vertically-oriented tube capped with a rubber septum and a horizontal tube connected to a source of dry nitrogen and vacuum, is charged with 10.0 g (37.9 mmol) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethyl chloride (Note 2). The assembled apparatus is evacuated and refilled with nitrogen three times. Freshly distilled diethyl ether (200 mL) (Note 3) is added to the flask by means of a double-ended needle (0.5 m in length) inserted through the vertical tube of the stopcock while a slight vacuum is applied to the apparatus. A slightly positive pressure of nitrogen is then maintained in the apparatus throughout the course of the reaction. The solution is cooled in a dry ice-acetone bath (Note 4). The glass jacket (or styrofoam cup) (Note 1), which surrounds the addition funnel, is filled with powdered dry ice, and 33 mL of a 2.3 M solution of tert-butyllithium (76 mmol) in pentane (Note 5) is added to the addition funnel by means of a syringe. After 10 min the lithium reagent is added dropwise to the flask over a period of 1 hr, while the temperature of the reaction mixture is maintained below -60°C. The solution of the resulting aryllithium reagent 1 is then used in either of the two reactions described below.

B. 4,5-Methylenedioxybenzocyclobutene. The reaction mixture from Part A is simply allowed to warm to room temperature over a period of several hours, during which time a white precipitate forms. After 18 hr, 100 mL of water is slowly added and the mixture is transferred to a 500-mL separatory funnel. As the mixture is shaken, the solid dissolves in the aqueous phase, which becomes light brown. The aqueous layer is extracted with two 75-mL portions of diethyl ether, and the combined organic layers are reduced in volume to 150 mL by rotary evaporation, washed with 75 mL of water and then 75 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to dryness by rotary evaporation to give 5.6 g of pale yellow solid (Note 6). This crude product is transferred to a large, dry ice-cooled sublimation apparatus (Note 7) and sublimed over a 6 hr period at 35°C (0.07 mm) at which time a dark brown oil remains in the bottom of the apparatus. The vacuum is released by filling the apparatus with nitrogen, and the cooled portion of the apparatus is allowed to warm to room temperature. Pure 4,5-methylenedioxybenzocyclobutene, 2 (5.1-5.2 g, 91-93%) is obtained as colorless crystals, mp 60-62°C (Note 8).

C. 1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline. The reaction mixture containing the aryllithium intermediate is stirred for 15 min (internal temperature -65 to -68°C), and then 4.3 mL (42 mmol) of distilled benzonitrile is added quickly. The mixture is allowed to warm gradually to room temperature and the stirring is continued overnight. The yellow solution (Note 9) is diluted with 25 mL of ether, the mixture is poured into a 1-L separatory funnel, and the reaction flask is rinsed with an additional 75 mL of ether. The combined ether solutions are washed with 150 mL of water and then extracted with three 75-mL portions of 10% (w/w) hydrochloric acid. The combined acid extracts are made basic by the addition of 100 mL of 20% (w/w) aqueous sodium hydroxide solution, and the resulting milky white mixture is extracted with three 75-mL portions of dichloromethane. The combined organic extracts are washed with 50 mL of water and 50 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness by rotary evaporation, to give 8.96 g (94% crude yield) of orange-tan solid.

This material is purified by recrystallization from ethyl acetate:acetone 2:1 (v:v) to give a first crop (6.8 g), and by flash chromatography[3] of the residue from the mother liquor, using 150 g of 230-400 mesh silica gel (Merck), a 40-mm diameter column, and elution with 10:1 (v:v) ethyl acetate:methanol. A fast moving orange band and a slower moving lemon-yellow band can be clearly seen on the column. The lemon-yellow band is collected from the column and evaporation gives a second crop (1.4 g) of comparably pure material. The total yield of the pale yellow isoquinoline is 8.2 g (86%), mp 135-137°C (Note 10).

2. Notes

1. The checkers used a home-made, glass-jacketed funnel sealed with a rubber septum. The submitters cut one side and part of the bottom of a styrofoam cup and with tape held this in place around the lower part of the addition funnel.

2. This starting material is prepared in three steps from commercially available (from Research Organic/Inorganic Chemical Corp., Belleville, NJ) 3,4-methylenedioxyphenylacetic acid according to well-established procedures that have been applied to similar compounds.[4] First, 16.0 g (88.8 mmol) of the acid, recrystallized from chloroform, is dissolved in 50 mL of tetrahydrofuran, and the solution is added to a suspension of 5.98 g (158 mmol) of lithium aluminum hydride powder in 225 mL of distilled diethyl ether (Note 3) at 0°C. *[Caution: Lithium aluminum hydride is very sensitive to mechanical shock and very reactive towards moisture and other protic substances; its dust is very irritating to skin and mucous membranes. It should not be allowed to come into contact with metallic species or apparatus, including metal*

spatulas, because of the potential danger of metal ion-promoted detonation.] The mixture is stirred at 25°C for 16 hr and is then quenched[5] by the careful, dropwise addition of 6 mL of 15% aqueous sodium hydroxide, and finally 18 mL of water. *[Caution: The reaction of excess lithium aluminum hydride with water is very exothermic and produces a large volume of hydrogen gas.]* The resulting mixture is stirred for 1 hr and is then subjected to vacuum filtration. The white solid which is retained is washed with three 50-mL portions of diethyl ether, and the combined filtrates are concentrated by rotary evaporation to give 13.1 g (89%) of 2-(3',4'-methylenedioxyphenyl)-ethanol as a clear, yellow oil, bp 136-140°C (0.003 mm). Next, 12.7 g (76.5 mmol) of this compound and 7.4 mL (91.5 mmol) of pyridine are dissolved in 200 mL of dichloromethane at 0°C, and 4.3 mL (83.9 mmol) of neat bromine is added to the solution over a 4-min period. After the solution has been stirred at 25°C for 16 hr, it is washed with three 50-mL portions of 2N hydrochloric acid, two 50-mL portions of saturated aqueous sodium sulfite, two 50-mL portions of water, and 50 mL of saturated aqueous sodium chloride. The organic layer is then dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to give 18.6 g (99.5%) of yellow solid. Recrystallization from a mixture of 160 mL of hexane and 60 mL of ethyl acetate gives 14.6 g (78%) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethanol as light yellow needles: mp 93-94°C. Finally, 9.95 mL (123 mmol) of distilled pyridine and 8.75 mL (120 mmol) of distilled thionyl chloride are added separately to a solution of 14.4 g (58.8 mmol) of the preceeding product and 180 mL of chloroform at 25°C. The mixture is heated at reflux for 18 hr, cooled to 25°C, washed with 40 mL of 1 N hydrochloric acid, 40 mL of 5% aqueous sodium carbonate, two 40-mL portions of water, and 40 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give 14.0 g (90%) of brown crystals. Distillation gives 13.0 g (84%) of an oil (bp 130-134°C at 0.006 mm), which solidifies to give the final product as colorless crystals: ^{1}H-NMR ($CDCl_3$) δ: 3.08 (t, 2 H, J = 6.8), 3.67 (t, 2 H, J = 6.8), 5.95 (s, 2 H), 6.74 (s, 1 H), and 6.98 (s, 1 H); mp 47.0-47.5°C (corrected).

3. Commercially available anhydrous diethyl ether is distilled under nitrogen from a solution of the sodium benzophenone radical anion generated by treating a solution of 10 g of benzophenone and 1 L of ether with 10 g of sodium ribbon until a dark blue or purple color persists.

4. Although the dry ice-acetone bath itself attains a temperature of -78°C, the lowest temperature achieved by the solution within the flask is only -68°C.

5. *Caution: tert-Butyllithium is pyrophoric in air; excess quantities of the reagent in the syringe should be discarded very carefully.* The checkers used the reagent available from Aldrich Chemical Company Ltd., England and standardized it by double titration with ethylene dibromide and hydrochloric acid.[6]

6. The submitters also ran the reaction on smaller scales using from 0.5 g to 5.0 g of starting material and regularly obtained a crude yield at this stage of 98-105%.

7. The sublimation apparatus should have at least a 1-cm separation between the upper surface of the crude solid to be sublimed and the bottom of the cooling surface in order to avoid splattering of the oily residue onto the purified product near the end of the sublimation procedure.

8. The product showed the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 3.00 (s, 4 H), 5.75 (s, 2 H), and 6.50 (s, 2 H).

9. At this stage, the submitters had a brick-red reaction mixture which became yellow on dilution with ether.

10. The product showed the following spectral properties: ^{1}H-NMR ($CDCl_3$) δ: 2.67 (t, 2 H, J = 7.5), 3.73 (t, 2 H, J = 7.5), 5.83 (s, 2 H), 6.63 (s, 2 H), and 7.37 (m, 5 H).

3. Discussion

The halogen-metal exchange reaction was pioneered by Gilman and coworkers[7] who established that substituted aryl bromides would exchange efficiently with n-butyllithium and that the reaction was of synthetic value provided that the substituent was not reactive toward alkyl- or aryllithium reagents. More recently, Parham[4e,8] and others[4f,9] further defined the scope and limitations of this reaction by demonstrating that haloarenes substituted with electron-withdrawing (CO_2H, CN, CO_2R) or electron-donating [OR, OCH_2O, $\leftarrow CH_2 \rightarrow_n X$, where X = Br, Cl] functional groups would selectively exchange with alkyllithium reagents at low temperature. While a detailed mechanistic evaluation is not within the scope of this discussion, the halogen-metal exchange reaction has been shown to be reversible and rapid at -75°C and, in the exchange of alkyllithium with a haloarene, the equilibrium reaction favors formation of the lithioarene.[7,10,11]

As exemplified in the present procedure, the reaction has been optimized and extended in scope; it affords functionalized benzocyclobutenes as well as substituted isoquinolines in high yields. Benzocyclobutenes have been used as intermediates in the synthesis of many naturally occurring alkaloids,[12] steroids,[13] polycyclic terpenoids,[14] and anthracycline antibiotics.[15] The traditional routes leading to the preparation of benzocyclobutenes have been reviewed[16] and have involved: (1) Cava's cyclization of o-quinodimethane intermediates (via reaction of sodium iodide with α,α,α',α'-tetrabromo-o-xylene), (2) thermal extrusion of sulfur dioxide from 1,3-dihydroisothianaphthene 2,2-dioxide, (3) dehydrogenation of the Diels-Alder adducts of 1,4-butadienes and cyclobutenes, and (4) Wolff rearrangement of α-diazoindanones. More recent methods include: (1) thermal rearrangement of p-tolylcarbene,[17] (2) thermal decomposition of 3-isochromanones,[12] and (3) cobalt-catalyzed cyclizations of acetylenic compounds.[18] Many of these methods for synthesizing functionalized benzocyclobutenes involve (a) multi-step routes, (b) unusual or relatively unavailable starting materials, (c) low overall yields, or (d) special apparatus. The method of halogen-metal exchange demonstrates a high degree of selectivity for formation of the lithioarene intermediate, is broad in scope without loss of procedural simplicity, and provides a high-yield route to benzocyclobutenes of general synthetic utility by direct cyclization of readily available 2-(2'-lithiophenyl)ethyl chlorides.[4e,f,9b]

The lithioarene intermediate has also been shown to be of use in the synthesis of the isoquinoline ring system. This ring system is common to a variety of natural products which possess useful physiological activity. Several methods have been developed for the synthesis of isoquinolines, the most commonly used routes being the Bischler-Napieralski and the Pictet-Spengler reactions.[19,20] These methods involve electrophilic, aromatic substitution in the key ring-forming steps with the limitation that best results are obtained only when the aromatic ring bears electron-donating substituents. The present method permits use of substrates either with or without electron-donating groups on the aromatic nucleus since generation of the lithioarene has been shown to be relatively independent of the nature of the substituents.[8a,d]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4,5-Methylenedioxybenzocyclobutene: Cyclobuta[*f*]-1,3-benzodioxole, 5,6-dihydro- (10); (61099-23-8)

1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline: 1,3-Dioxolo[4,5-*g*]isoquinoline, 7,8-dihydro-5-phenyl- (10); (55507-10-3)

3,4-Methylenedioxyphenylacetic acid: Acetic acid, [3,4-(methylenedioxy)phenyl]- (8); 1,3-Benzodioxole-5-acetic acid (9); (2861-28-1)

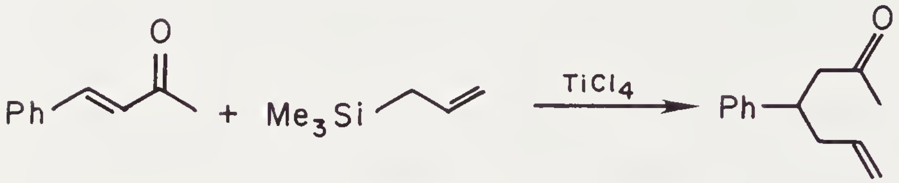
Thionyl chloride (8,9); (7719-09-7)

tert-Butyllithium: Lithium, tert-butyl- (8); Lithium, (1,1-dimethylethyl)- (9); (594-19-4)

Benzonitrile (8,9); (100-47-0)

CONJUGATE ALLYLATION OF α,β-UNSATURATED KETONES WITH ALLYLSILANES: 4-PHENYL-6-HEPTEN-2-ONE

(6-Hepten-2-one, 4-phenyl-)



Submitted by Hideki Sakurai, Akira Hosomi, and Josabro Hayashi[1].

Checked by Todd A. Blumenkopf and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask is fitted with a dropping funnel (Note 1), mechanical stirrer, and reflux condenser attached to a nitrogen inlet. In the flask are placed 29.2 g (0.20 mol) of benzalacetone (Note 2) and 300 mL of dichloromethane (Note 3). The flask is immersed in a dry ice-methanol bath (-40°C) and 22 mL (0.20 mol) of titanium tetrachloride (Note 4) is slowly added by syringe to the stirred mixture. After 5 min, a solution of 30.2 g (0.26 mol) of allyltrimethylsilane (Notes 5 and 6) in 300 mL of dichloromethane is added dropwise with stirring over a 30-min period. The resulting red-violet reaction mixture is stirred for 30 min at -40°C (Note 7), hydrolyzed by addition of 400 mL of H_2O and, after the addition of 500 mL of ethyl ether with stirring, allowed to warm to room temperature. The nearly colorless organic layer is separated and the aqueous layer is extracted with three 500-mL portions of ethyl ether. The organic layer and ether extracts are combined and washed successively with 500 mL of saturated sodium bicarbonate and 500 mL of saturated sodium chloride, dried over anhydrous sodium sulfate and evaporated at reduced pressure. The residue is distilled under reduced pressure through a 6-inch Vigreux column to give 29.2-30.0 g (78-80%) of 4-phenyl-6-hepten-2-one, bp 69-71°C (0.2 mm), n_D^{20} 1.5156, as a colorless liquid (Note 8).

2. Notes

1. A 500-mL dropping funnel, with pressure-equalizing arm, is used.

2. Benzalacetone is purchased from Wako Pure Chemical Ind., Ltd., or Aldrich Chemical Company, Inc.

3. Dichloromethane is dried over anhydrous calcium chloride, distilled, and stored over 5Å molecular sieves before use. The checkers distilled dichloromethane from calcium hydride immediately before use.

4. Titanium tetrachloride, purchased from Junsei Chemical Co., Ltd., is distilled before use. The checkers purchased titanium tetrachloride from the Fisher Scientific Company, and distilled it from copper powder before use.

5. The starting allyltrimethylsilane can be prepared in satisfactory yield by the procedure of Sommer.[2] It can also be purchased from PCR Inc., Aldrich Chemical Company, Inc., Fluka A. G., Petrarch Systems Inc., and Tokyo Kasei Kogyo Co., Ltd. The checkers employed material from Petrarch.

6. The use of more than 1.2 equiv of allyltrimethylsilane is essential for shortening the reaction time as well as to avoid contamination of the product by unreacted benzalacetone.

7. Disappearance of benzalacetone and appearance of product can be readily monitored by thin layer or gas chromatographic analysis on a 1-m column packed with 20% Silicone SE-30 at 180°C. The reaction should be stopped as soon as disappearance of benzalacetone is confirmed.

8. Gas chromatographic analysis of the product on a 1-m column packed with 20% Silicone SE-30 at 180°C should give a single peak. The product has the following spectral properties: IR (film) cm^{-1}: 1710, 1630 (C=C); ^1H NMR ($CDCl_3$) δ: 1.97 (s, 3 H, CH_3CO), 2.35 (t, 2 H, J = 7.5, $CH_2C=C$), 2.72 (d, 2 H, J = 7.5, CH_2CO), 3.27 (quintet, 1 H, J = 7.5, PhCH), 4.8-5.1 (m, 2 H, $CH_2=C$), 5.4-5.9 (m, 1 H, CH=C), 7.0-7.4 (m, 5 H, aromatic).

3. Discussion

This procedure is general for the conjugate allylation of α,β-unsaturated ketones with allysilanes.[3] Some representative examples are listed in Table I. The main advantages of the method are its wide generality and the ready availability of the necessary starting materials. The procedure is often useful for the preparation of δ,ε-unsaturated ketones that cannot be obtained in satisfactory yield by the use of allylcuprate (e.g., entry 13) reagents.[4] Another useful aspect of the reaction is the regiospecific coupling of the allyl group. Examples of this feature can be seen in entries 2 and 5. Although cyclic as well as acyclic α,β-unsaturated ketones give satisfactory results, the reaction is slower in sterically hindered systems (entries 13 and 14). However, even in these cases, good yields are obtained by using excess allylsilane and by conducting the reaction at higher temperature. Since the allyl group can be modified by the regioselective addition of various reagents to the double bond,[5,6] the method is applicable to the synthesis of a wider variety of compounds than are shown in the Table. By oxidation of the double bond 1,5-diketones may be obtained.[7] Conjugate allylation with allylsilanes can be used in conjunction with a suitable electrophile to achieve "one-pot" double alkylation at the adjacent vinyl position of an α,β-unsaturated ketone.[8] The method has also been utilized in the synthesis of perhydroazulenones.[9] Allylsilanes also undergo regioselective, Lewis acid-catalyzed reaction with carbonyl compounds,[10] acetals,[11] α,β-unsaturated acetals,[12] acyl halides,[13] tertiary alkyl halides,[14] and oxiranes.[14] Such allylations can also be achieved by using allystannanes.[15]

1. Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan.
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TABLE I

CONJUGATE ALLYLATION OF α,β-ENONES WITH ALLYLSILANES PROMOTED BY TITANIUM TETRACHLORIDE[a]

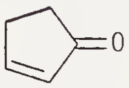
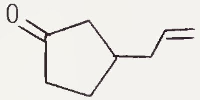
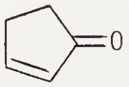
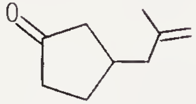
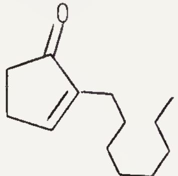
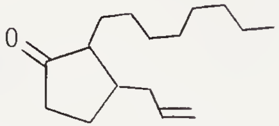
		Conditions			
Entry	Allylsilane	α,β-Enone	Temp., °C, time	δ,ε-Enone (% yield)[b]	
1	(I)[c]	$CH_2=CHCOCH_3$	-78, 1 min	$CH_2=CH(CH_2)_3COCH_3$	(59)
2	(II)[d]	$CH_2=CHCOCH_3$	-78, 3 hr	$CH_2=CHC(CH_3)_2CH_2CH_2COCH_3$	(79)
3	(I)	$(CH_3)_2C=CHCOCH_3$	25, 5 min	$CH_2=CHCH_2C(CH_3)_2CH_2COCH_3$	(87)
4	(III)[e]	$PhCH=CHCOCH_3$[f]	-78, 0.5 min	$CH_2=C(CH_3)CH_2CH(Ph)CH_2COCH_3$	(69)
5	(IV)[g]	$PhCH=CHCOCH_3$	-78, 5 hr	$CH_2=CHCH(CH_3)CH(Ph)CH_2COCH_3$	(76)
6	(I)	$PhCH=CHCOPh$	-78, 1 min	$CH_2=CHCH_2CH(Ph)CH_2COPh$	(96)
7	(I)		-78, 2 hr		(70)
8	(III)		-78, 10 min		(70)
9	(I)		-78, 2 hr		(54)

TABLE I (contd.)

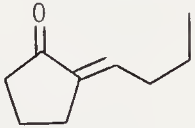
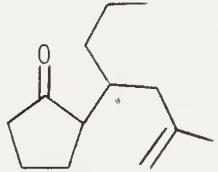
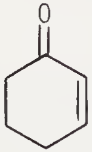
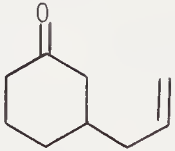
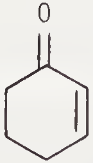
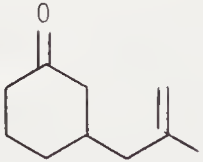
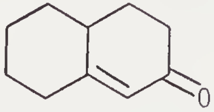
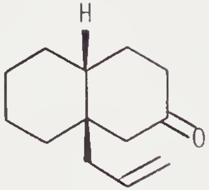
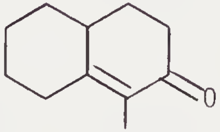
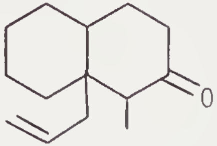
10	(III)		-78, 30 min		(82)[h]
11	(I)		-78, 1 hr		(80)[i]
12	(III)		-78, 10 min		(99)
13	(I)[j]		-78, 18 hr then -30, 5 hr		(85)[k]
14	(I)		-78, 2 hr then 0, 15 min		(88)

TABLE I (contd.)

[a]The reaction was carried out on a 1-20 mmol scale in dichloromethane. [b] Yields after isolation by distillation or thin layer chromatography. [c](I): $Me_3SiCH_2CH=CH_2$. [d](II): $Me_3SiCH_2CH=C(CH_3)_2$. [e](III): $Me_3SiCH_2C(CH_3)CH_2$. [f]Three equivalents of the allylsilane were used. [g](IV): trans-$Me_3SiCH_2CH=CHCH_3$. [h]A [2+2] cycloadduct assigned the structure 1-methyl-1-trimethylsilylmethyl-3-n-propylspiro[3.4]octan-5-one was obtained in 19% yield. [i]B.p. 56-60°C (3 mm), n_D^{20} 1.4719. [j]Two equivalents of the allysilane were used. [k]B.p. 83-85°C (0.6 mm), n_D^{20} 1.5111. A diallylated product assigned the structure 2,8a-diallyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene was obtained as a forerun in less than 5% yield.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

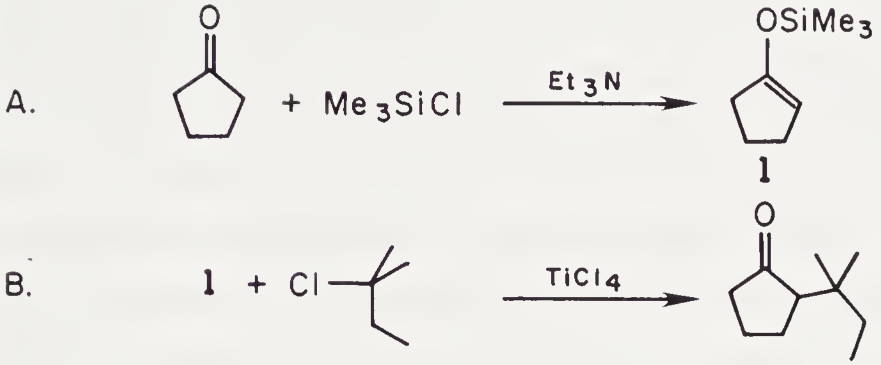
4-Phenyl-6-hepten-2-one: 6-Hepten-2-one, 4-phenyl- (10); (69492-29-1)

Benzalacetone: 3-Buten-2-one, 4-phenyl- (8,9); (122-57-6)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

Allyltrimethylsilane: Silane, allyltrimethyl- (8); Silane, trimethyl-2-propenyl- (9); (762-72-1)

α-tert-ALKYLATION OF KETONES:
2-tert-PENTYLCYCLOPENTANONE
(Cyclopentanone, 2-(tert-pentyl-)



Submitted by M. T. Reetz, I. Chatziiosifidis, F. Hubner, and H. Heimbach[1].
Checked by Kevin Kunnen and Carl R. Johnson.

1. Procedure

A. 1-Trimethylsilyloxycyclopentene.[2] A 1-L, two-necked, round-bottomed flask is equipped with a mechanical stirrer and a reflux condenser having a drying tube (calcium chloride). The flask is charged with 200 mL of dimethylformamide (Note 1), 45 g (0.54 mol) of cyclopentanone (Note 2), 65.5 g (0.6 mol) of chlorotrimethylsilane (Note 2) and 185 mL (1.33 mol) of triethylamine (Note 1), and the mixture is refluxed for 17 hr (Note 3). The mixture is cooled, diluted with 350 mL of pentane, and washed four times with 200-mL portions of cold saturated aqueous sodium hydrogen carbonate. The aqueous phases are extracted twice with 100-mL portions of pentane and the combined organic phases are washed *rapidly* with 100 mL of ice-cold aqueous 2 N HCl and immediately thereafter with a cold saturated solution of sodium hydrogen carbonate. After the mixture has been dried over anhydrous magnesium sulfate, the pentane is removed by rotary evaporation. Distillation of the oily residue at 60°C (12 mm) using a 20-cm Vigreux column affords 50.1-51.6 g (60-62%) of 1-trimethylsilyloxycyclopentene (1) as a colorless liquid (Note 4).

B. 2-tert-Pentylcyclopentanone. A dry, 250-mL, three-necked, round-bottomed flask is fitted with a gas inlet, a gas bubbler, rubber septum and magnetic stirrer. The apparatus is flushed with dry nitrogen or argon and charged with 120 mL of dry dichloromethane (Note 5), 15.6 g (0.10 mol) of 1-trimethylsilyloxycyclopentene and 11.7 g (0.11 mol) of 2-chloro-2-methylbutane (Note 6). The mixture is cooled to -50°C (Note 7) and a cold (-50°C) solution of 11 mL (0.10 mol) of titanium tetrachloride (Note 8) in 20 mL of dichloromethane is added within 2 min through the rubber septum with the aid of a syringe. During this operation rapid stirring and cooling is maintained. Sunlight should be avoided. The reddish-brown mixture is stirred at the given temperature for an additional 2.5 hr and is then rapidly poured into 1 L of ice water (Note 9). After the addition of 400 mL of dichloromethane, the mixture is vigorously shaken in a separatory funnel; the organic phase is separated and washed twice with 400-mL portions of water. The aqueous phase of the latter two washings is extracted with 200 mL of dichloromethane; the organic phases are combined and dried over anhydrous sodium sulfate. The mixture is concentrated using a rotary evaporator and the residue is distilled at 80°C (12 mm) (Note 10) to yield 9.2-9.5 g (60-62%) (Note 11) of 2-tert-pentylcyclopentanone as a colorless oil (Note 12).

2. Notes

1. Dimethylformamide and triethylamine were purchased from Baker (Baker Analyzed Reagent) and used without further purification.

2. Cyclopentanone and chlorotrimethylsilane were purchased from Aldrich Chemical Company and used without further purification.

3. According to the original procedure of House,[2] only four hours are needed, affording a 59% yield. However, the submitters found that an increase in reaction time raises the yield.

4. The spectral properties of the compound are as follows: ^1H NMR (CCl_4) δ: 0.2 (s, 9 H), 1.6-2.4 (m, 6 H), 4.4 (m, 1 H); IR (film) 1645 cm^{-1} (lit.[2] 1645 cm^{-1}).

5. Reagent grade dichloromethane is dried by passing over a column of aluminum oxide (activity I).

6. The submitters purchased 2-chloro-2-methylbutane from Eastman Kodak Company. The checkers prepared the halide as follows. A separatory funnel was charged with 21.5 mL (0.2 mol) of 2-methyl-2-butanol and 100 mL of concd hydrochloric acid. The mixture was shaken vigorously with periodic venting for 10 min. The layers were separated and the 2-chloro-2-methylbutane layer (upper) was washed several times with equal volumes of cold water. The product was dried over calcium chloride and distilled, bp 85°C.

7. The precise temperature is not critical. The checkers observed that the reaction proceeds in about the same time and yield at -78°C. However, at temperatures above -40°C a drop in yield may occur.

8. The titanium tetrachloride should be clean, colorless, and free of hydrogen chloride. The checkers used material freshly distilled in an argon atmosphere.

9. If sodium bicarbonate is used, large amounts of titanium oxide-containing emulsions tend to form which hamper the purification of the product.

10. The by-products consist of volatile cyclopentanone and an unknown high boiling material, so that rapid vacuum transfer at room temperature and 0.02 mm is also possible. Extremely slow distillation at high temperatures should be avoided. The value of 72°C (2.2 mm) cited in the literature[3] seems to be in slight error.

11. The submitters ran the reaction on a 0.5 scale and reported yields of 63-68%.

12. The product is > 96% pure as checked by gas chromatography (4% UCON LB 550X, Chromosorb G, AW-DMCS 80-100 mesh, 130°C). The spectral properties are as follows: IR (neat) cm^{-1}: 3050-2800, 1735, 1460, 1150; ^1H NMR (CCl_4) δ: 0.80 (J = 6 Hz, CH_3 of the ethyl group, which partially overlaps with the signals of the other two diastereotopic methyl groups), 0.82 (s), 0.92 (s), 1.15-2.25 (m); ^{13}C NMR ($CDCl_3$) δ: 7.78, 19.87, 23.72 (slightly broad), 25.57, 32.62, 34.70, 40.02, 55.39, 219.57.

3. Discussion

This procedure solves the long-pending problem of α-tert-alkylation of ketones. The generality is shown by the fact that a wide variety of structurally different ketones can be alkylated via the corresponding silyl enol ethers with good yields.[4] Variation of the alkylating agent is also possible, branched and cyclic tertiary akyl halides reacting position specifically without signs of rearrangement.[4] Chemoselectivity studies reveal that esters, aromatic groups, and primary alkyl halide moieties are tolerated.[4] In the case of a sensitive enol ether such as that derived from acetone, titanium tetrachloride should be replaced by more mild Lewis acids such as zinc chloride, although the yields are lower.[5] Finally, it should be noted that any S_N1-reactive alkyl halide is likely to be a suitable alkylating agent in Lewis acid promoted α-alkylation of carbonyl compounds. Indeed, aryl-activated secondary alkyl halides react in the same way.[6] Generally, such alkylating agents are unsuitable in classical enolate chemistry because of the ease of hydrogen halide elimination and/or the failure to react regiospecifically. The methods are thus complementary.

A related tert-butylation procedure in which the silyl enol ether is added to a mixture of titanium tetrachloride and tert-butyl chloride gives rise to distinctly lower yields.[7,8] This is also the case if the tertiary halide is added to a mixture of silyl enol ether and titanium tetrachloride.[5]

A number of alternative multi-step procedures for the synthesis of α-tert-alkyl ketones are known, none of which possess wide generality. A previous synthesis of 2-tert-pentylcyclopentanone involved reaction of N-1-cyclopentenylpyrrolidine with 3-chloro-3-methyl-1-butyne and reduction of the resulting acetylene (overall yield 46%).[3] However, all other enamines tested afford much lower yields.[3] Cuprate addition to unsaturated ketones may be useful in certain cases.[9] Other indirect methods have been briefly reviewed.[5]

1. Fachbereich Chemie der Universität, Hans-Meerwein-Strasse, 3550 Marburg, West Germany.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-tert-Pentylcyclopentanone: Cyclopentanone, 2-tert-pentyl (8,9); (25184-25-2)

Cyclopentanone (8,9); (120-92-3)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

1-Trimethylsilyloxycyclopentene: Silane, (1-cyclopenten-1-yloxy)trimethyl- (8,9); (19980-43-9)

2-Chloro-2-methylbutane: Butane, 2-chloro-2-methyl- (8,9); (594-36-5)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

PREPARATION OF HALIDE-FREE METHYLLITHIUM

(Lithium, methyl-)

$$CH_3Cl + Li(1\%\,Na) \xrightarrow[25^\circ C]{Ether} CH_3Li + LiCl$$

Submitted by Michael J. Lusch, William V. Phillips, Ronald F. Sieloff, Glenn S. Nomura, and Herbert O. House[1].

Checked by Gregory S. Bisacchi and Robert V. Stevens.

1. Procedure

Caution! The fine lithium dispersion used in this preparation, once washed to remove the mineral oil coating, will ignite spontaneously if exposed to air. Also, the methyl chloride and ether used are very volatile and highly flammable. The entire preparation including the disposal of any residual lithium should be performed in an efficient hood with a safety shield in front of the apparatus. A suitable dry-powder fire extinguisher should be kept at hand to extinguish any fires resulting from the accidental spillage of the washed lithium dispersion or of the methyllithium solution.

A dry 1-L, three-necked, round-bottomed flask equipped with a large Teflon-covered magnetic stirring bar, a thermometer, and a dry ice condenser (Note 1) is flushed with argon (Note 2), then capped with a serum stopper and subsequently maintained under a positive pressure of argon (Note 3). A 30% dispersion of lithium metal (in mineral oil) containing 1% sodium (13.9 g, 2.00 g-atom of lithium) (Note 4) is rapidly weighed and transferred to the flask.

The lithium is washed three times by transferring approximately 150-mL portions of anhydrous ethyl ether (Note 5) into the flask through the serum stopper by forced siphon through a stainless steel cannula, stirring the resulting suspension of lithium briefly, allowing the lithium to rise to the surface, and finally withdrawing the major part of the underlying ether by forced siphon through a cannula. Anhydrous ethyl ether (500 mL) is added to the resultant oil-free lithium. Methyl chloride gas (bp -24°C, $d^{-24°C}$ 0.99 g/mL) from a compressed gas cylinder is passed through a flask containing 4Å molecular sieves and into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry ice condenser, and cooled to -24°C with a bath of dry ice-acetone (Fig. 1). When 52.7 mL (52.5 g, 1.04 mol) of liquid methyl chloride has been collected, the adapter and condenser are removed, several boiling chips are added to the cold (-24°C) graduated cylinder, and the cylinder is stoppered with a rubber septum through which is inserted a stainless steel cannula. The other end of this cannula is inserted through the rubber septum of the flask so that its tip is just above the liquid surface of the reaction flask. Dry ice-acetone is then added to the condenser attached to the reaction flask. Vigorous stirring of the ethereal lithium dispersion is begun and the methyl chloride is added over approximately a 1.5-hr period. The rate at which methyl chloride is distilled into the reaction vessel is controlled by slight cooling or warming of the graduated cylinder which contains the liquid methyl chloride. During addition, the initial grey suspension changes to a brown to purple suspension; by the end of the addition, little if any lithium metal should be seen floating on the surface of the ether solution when stirring is interrupted. After the addition of methyl chloride is complete, the reaction mixture is stirred at 25°C for an additional 0.5-1 hr and then allowed to stand overnight or longer (Note 6) at 25°C under a static argon atmosphere, whereupon the precipitated lithium chloride settles to the bottom of the flask. The dry ice condenser and thermometer are removed from the flask and replaced with rubber septa. The supernatant methyllithium solution is transferred by forced siphon using a large-guage cannula through a glass wool pad (Note 7) into a receiving flask previously flushed with an inert gas (Fig. 2). The receiving flask which contains the filtrate, a pale yellow solution of methyllithium, is removed (Note 8) and stored in a refrigerator for 12-24 hr during which time an additional small quantity of lithium chloride separates as fine crystals. The resulting supernatant solution is transferred with a stainless steel cannula and a slight positive pressure of argon or nitrogen into one or more suitable oven-dried nitrogen-filled storage bottles capped with rubber septa. Two 1-mL aliquots of the solution are removed with a hypodermic syringe for a modified Gilman titration (Note 9) and a 5-mL aliquot is removed with a hypodermic syringe to determine the halide concentration (Note 10). The solution contains 1.40-1.77 M methyllithium accompanied by 0.07-0.09 M lithium chloride corresponding to a 70-89% yield of methyllithium. If this solution is protected from oxygen and moisture, it may be stored at 0-25°C for several months (and remain active).

2. Notes

1. The dry ice condenser used with the apparatus should have sufficient condensing capacity to prevent the loss of significant amounts of methyl chloride; a condenser 38 cm long and 3.8 cm in diameter was suitable.

2. Since finely divided lithium floats on the surface of the solvent and will be in contact with the atmosphere in the reaction vessel, an argon atmosphere, rather than a nitrogen atmosphere, should be used to avoid formation of the insoluble reddish-brown lithium nitride.

3. A slight positive pressure of argon was maintained in the vessel throughout the reaction by using an argon line connected to both a bubbler containing Nujol and the inlet on the dry ice condenser.

4. A dispersion in mineral oil of 30% (by weight) of lithium containing 1% by weight of sodium is marketed by Alfa Products, Morton/Thiokol, Inc. This oil-coated dispersion may be exposed to the air during transfer and weighing and is conveniently transferred from its container by pouring through a wide-mouth funnel. Small quantities of the dispersion which adhere to the apparatus may be disposed of by rinsing in a stream of warm water to lower the viscosity of the oil and allow the suspended lithium to react with water at a controlled rate. To dispose of large quantities of this dispersion (or any quantity of lithium powder no longer coated with oil), the material should be suspended in anhydrous ether under an argon atmosphere and t-butyl alcohol should be added dropwise to the suspension until all of the lithium metal has been consumed. Since hydrogen is liberated during these disposal procedures, they should be performed in an efficient hood.

5. Anhydrous ethyl ether was distilled from lithium aluminum hydride immediately before use.

6. Although most of the lithium chloride separates from the ether solution as a finely divided solid during the reaction, additional small quantities of lithium chloride continue to separate for 12-14 hr. After standing overnight, a typical reaction contains a precipitate of finely divided brownish-pink solid below a clear, pale yellow solution.

7. A convenient filter was constructed by packing glass wool, previously dried in an oven, into a 20-mL Luer-lok syringe barrel fitted with a 15 gauge needle. The syringe barrel was capped with a serum stopper. A large diameter cannula (at least 15 gauge) should be used to transfer the methyllithium solution from the flask to the filter since smaller guage cannulae are frequently plugged by solid particles.

8. As soon as the receiver containing the methyllithium solution has been removed and stoppered, the residual solids in the reaction flask and the filtration apparatus should be rinsed into another receiver with anhydrous ether under an atmosphere of argon or nitrogen. The ether slurry of solids, which may contain some unchanged lithium metal, should be treated cautiously in a hood with t-butyl alcohol to consume any residual lithium metal before the mixture is discarded.

9. One 1-ml aliquot is added to 1.0 mL of freshly-distilled 1,2-dibromoethane (bp 132°C) in an oven-dried flask which contains a static atmosphere of nitrogen or argon. After the resulting solution has been allowed to stand at 25°C for 5 min, it is diluted with 10 mL of water and titrated for base content (residual base) to a phenolphthalein endpoint with standard 0.100 M hydrochloric acid. The second 1-mL aliquot is added cautiously to 10 mL of water and then titrated for base content (total base) to a phenolphthalein endpoint with standard aqueous 0.100 M hydrochloric acid. The methyllithium concentration is the difference between the total base and residual base concentrations.[2] Alternatively, the methyllithium concentration may be determined by titration with a standard solution of sec-butyl alcohol employing 2,2'-bipyridyl as an indicator.[3a,b]

10. To determine the concentration of chloride ion,[3c,d] a 5-mL aliquot of the methyllithium solution is cautiously added to 25 mL of water and the resulting solution is acidified with concentrated sulfuric acid and then treated with 2-3 mL of ferric ammonium sulfate [$Fe(NH_4)(SO_4)_2$ 12 • H_2O] indicator solution and 2-3 mL of benzyl alcohol. The resulting mixture is treated with 10.0 mL of standard aqueous 0.100 M silver nitrate solution and then titrated with standard aqueous 0.100 M potassium thiocyanate solution to a brownish-red endpoint.

3. Discussion

Although ethereal solutions of methyllithium may be prepared by the reaction of lithium wire with either methyl iodide[4] or methyl bromide[5] in ether solution, the molar equivalent of lithium iodide or lithium bromide formed in these reactions remains in solution and forms, in part, a complex with the methyllithium.[6] Certain of the ethereal solutions of methyllithium currently marketed by several suppliers including Alfa Products, Morton/Thiokol, Inc., Aldrich Chemical Company, and Lithium Corporation of America, Inc., have been prepared from methyl bromide and contain a full molar equivalent of lithium bromide. In several applications such as the use of methyllithium to prepare lithium dimethylcuprate[7] or the use of methyllithium in 1,2-dimethyoxyethane to prepare lithium enolates from enol acetates or trimethylsilyl enol ethers,[3b] the presence of this lithium salt interferes with the titration and use of methyllithium. There is also evidence which indicates that the stereochemistry observed during addition of methyllithium to carbonyl compounds may be influenced significantly by the presence of a lithium salt in the reaction solution.[8] For these reasons it is often desirable to have ethereal solutions of methyllithium that do not contain an equivalent amount of lithium iodide or lithium bromide.

The reaction of lithium with methyl chloride in ether solution produces a solution of methyllithium from which most of the relatively insoluble lithium chloride precipitates. Ethereal solutions of "halide-free" methyllithium, containing 2-5 mole percent of lithium chloride, were formerly marketed by Foote Mineral Company and by Lithium Corporation of America, Inc., but this product has been discontinued by both companies. Comparable solutions are also marketed by Alfa Products and by Aldrich Chemical Company; these solutions have a limited shelf-life and older solutions have often deteriorated badly even before the container is opened. Since an ether solution of methyl chloride reacts very slowly with lithium wire used in reactions with methyl bromide or methyl iodide, the present procedure[9] uses a finely divided suspension of lithium metal containing 1% (by weight) of sodium[6,10] to achieve a rapid reaction with methyl chloride. The finely divided lithium containing 1% sodium is marketed as a 30% (by weight) dispersion in mineral oil and must be washed free of this protective hydrocarbon diluent before use in order to avoid contamination of the final methyllithium reagent with a substantial amount of a mixture of high molecular weight hydrocarbons. Since lithium is less dense than common organic solvents such as diethyl ether or pentane, the washing procedure must be done with special care to avoid starting a fire with the pyrophoric, finely-divided lithium.[2b] Finely divided lithium with somewhat higher or lower percentages of sodium are expected to work equally well.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Methyl chloride: Methane, chloro- (8,9); (74-87-3)

Lithium (8,9); (7439-93-2)

Methyllithium: Lithium, methyl- (8,9); (917-54-4)

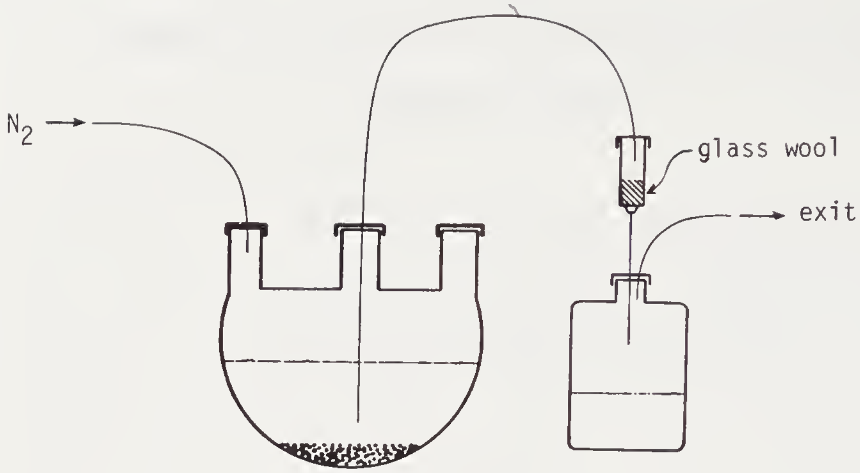


Figure 2. Decanting the methyllithium solution

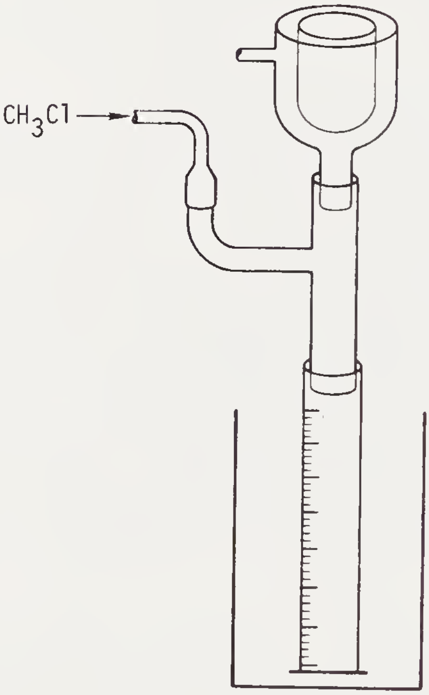
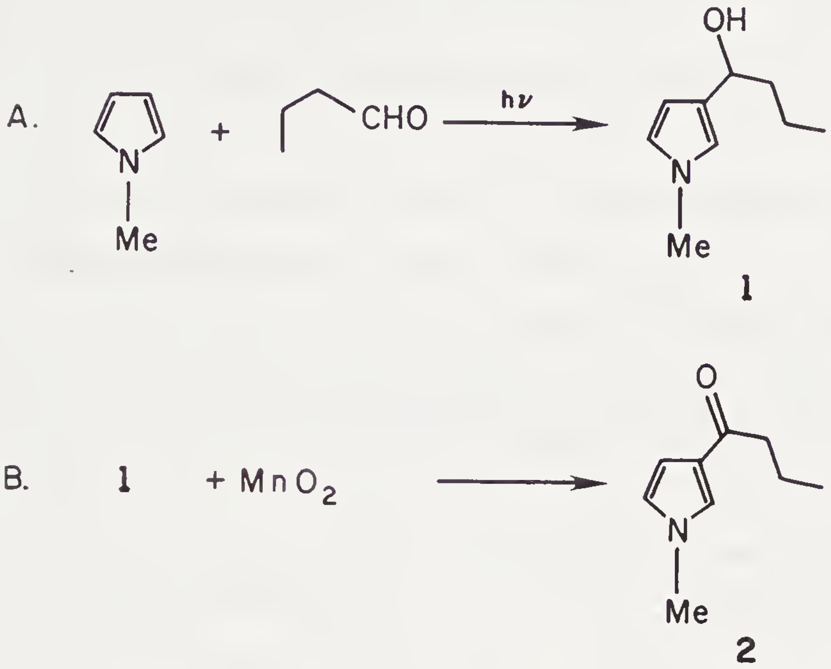


Figure 1. Condensing the methyl chloride

3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE AND 3-BUTYROYL-1-METHYLPYRROLE

(1H-Pyrrole-3-methanol, 1-methyl-α-propyl- and 1-Butanone, 1-(1-methyl-1H-pyrrol-3-yl)-)



Submitted by H. M. Gilow and G. Jones, II[1].

Checked by Steven M. Pitzenberger, Richard A. Hayes, and Orville L. Chapman.

1. Procedure

A. 3-(1-Hydroxybutyl)-1-methylpyrrole (**1**). A photochemical quartz immersion well (220 mm length) (Note 1) equipped with 450-watt Hanovia medium pressure mercury lamp and a Vycor filter, cooled with water, is used. To a 125-mL Pyrex reaction vessel (230 mm long, 64 mm i.d.) equipped with a gas inlet and outlet, is added 60 mL (55 g, 0.676 mol) of 1-methylpyrrole (Note 2) and 65 mL (54 g, 0.936 mol) of butyraldehyde (Note 3). Dry nitrogen is slowly bubbled through the solution during 48 hr of photolysis (Note 4).

The solution is concentrated under reduced pressure. The remaining oil is distilled under reduced pressure using a simple distillation apparatus. After a small forerun, 27 g (0.179 mol, 26% yield) (Note 5) of 1 is collected, as a light yellow oil, bp 90-94°C/0.05 mm (Note 6). Further purification is accomplished by a second distillation under reduced pressure, bp 90.2°C/0.05 mm (Notes 7 and 8).

B. 3-Butyroyl-1-methylpyrrole (**2**). A 100-mL, one-necked, round-bottomed flask is fitted with an efficient reflux condenser and arranged for magnetic stirring and heating. The flask is charged with 50 mL of pentane (Note 9) and 2.0 g (13 mmol) of 1 (Note 10). To the rapidly-stirred solution is added 16 g (180 mmol) of activated manganese(IV) oxide (Note 11) in small portions over 5 min. The solution is heated at reflux for 18 hr and then an additional 8 g (90 mmol) of activated manganese(IV) oxide is added in portions (Note 12). After being heated at reflux for 24 hr, the reaction mixture is filtered through a 2-cm Celite filter pad. The filtered manganese oxides are thoroughly washed with about 200-300 mL of dichloromethane. Evaporation of solvent from the combined filtrates leaves 1.4-1.6 g of a light yellow oil. Bulb-to-bulb distillation at 100°C/0.1 mm (Note 13) gives 1.27-1.40 g (8.4-9.3 mmol, 64-71% yield) of an oil (**2**) (Note 14).

2. Notes

1. The photochemical quartz immersion well was obtained from Ace Glass Inc.

2. 1-Methylpyrrole was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 112-112.5°C.

3. Butyraldehyde was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 74.5-75.5°C. It is important that a freshly distilled sample, free of trimer, be used, or the final product will be contaminated with trimer.

4. When the reaction mixture was monitored by GLC (500-mm x 3.2-mm column, packed with 5% OV 101 on chromosorb G, HP, 100/120 mesh) most of the product was formed in the first 24 hr of photolysis, as shown by the following profile:

Time of Photolysis	% of Alcohol (Based on Starting Pyrrole)
2 hr	4
19 hr	18
24 hr	23
48 hr	25

5. The checkers found that the distillate contained 15-30% butyraldehyde (as monitored by NMR), which depended upon the efficiency of the distillation. A 10-cm column packed with glass helices was the most efficient, but the yield of distilled product dropped drastically.

6. The susceptibility of 3-(1-hydroxybutyl)-1-methylpyrrole to air oxidation and decomposition with acid requires that prolonged storage be done in tightly capped containers in a refrigerator.

7. The spectral properties of 3-(1-hydroxybutyl)-1-methylpyrrole are as follows: ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, CH_3-C), 1.10-1.80 (m, 4 H, $-CH_2CH_2-$), 2.88 (s, 1 H, H-O-), 3.51 (s, 3 H, CH_3N-), 4.50 (t, 1 H, HC-), 5.9 (t, 1 H, 4-pyrrole) and 6.41 (d, 2 H, 2,5-pyrrole). IR (neat)cm^{-1}: 3400 (H-O stretch) and 1175 (C=O stretch).

8. The reaction can also be carried out using smaller amounts of 1-methylpyrrole (0.113 mol), butyraldehyde (0.113 mol) and a solvent (245 mL acetonitrile, ACS grade) in a somewhat larger reaction vessel. After 17 hr of photolysis, and after removal of the volatile material and distillation of the remaining oil under reduced pressure, 4-5 g of the alcohol is isolated.

9. The submitters used dichloromethane. The checkers found that use of pentane[2] resulted in increased yields for the oxidation.

10. When the alcohol (**1**) is contaminated with small amounts of butyraldehyde, oxidation proceeds with a much lower yield of product.

11. Activated manganese(IV) oxide was purchased from Alfa Products, Morton/Thiokol, Inc.

12. Progress of the reaction can be monitored by taking an aliquot of the reaction, filtering it, removing the solvent in a vacuum, dissolving the residual oil in carbon tetrachloride, and observing the ^1H NMR spectrum. Relative integration of the proton resonances of the pyrrole 2-position (6.1 ppm for the alcohol and 7.2 ppm for the ketone) gives an indication of the percent conversion. The checkers found only 77% conversion after the first reflux period. A higher conversion, 90-97%, was achieved after a second addition of activated manganese(IV) oxide and subsequent heating at reflux.

13. The submitters used a short path simple distillation apparatus; bp 85-87°C (0.2 mm).

14. The following spectral properties were recorded for 3-butyroyl-1-methylpyrrole, 2: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.97 (t, 3 H), 1.72 (sextet, 2 H), 2.68 (t, 2 H), 3.68 (s, 3 H), 6.6 (m, 2 H, 4,5-pyrrole), 7.23 (t, 1 H, 2-pyrrole); IR (neat) cm^{-1}: 1660 (C=O stretch); MS (70 eV) m/e (rel. int.): 151 (8.6, M^+), 123 (1.6), 108 (34), 28 (100). The submitters reported the following spectral data: ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3 H), 1.65 (sextet, 2 H), 2.65 (t, 2 H), 3.63 (s, 3 H), 6.47 (m, 2 H), 7.15 (m, 1 H); IR (neat) cm^{-1}: 1700.

3. Discussion

This procedure provides a method for functionalizing the pyrrole ring in the 3-position, normally a difficult synthetic step when conventional electrophilic substitution is used.[3] The technique has been extended to addition of several aldehydes and acetone and to a number of pyrroles.[4] The generality includes photoaddition to imidazoles which are substituted in the 4-position. Pyrrole photoadduct alcohols are readily dehydrated to 3-alkenylpyrroles or oxidized to 3-acyl derivatives.

The precedent is strong for the involvement of oxetanes as intermediates in carbonyl additions to pyrroles.[5-7] NMR evidence has been obtained for an oxetane adduct of acetone and N-methylpyrrole.[4] The initial photoadduct was shown to rearrange readily on workup to the 3-(hydroxyalkyl)pyrrole derivative.

Oxidation of the 3-(hydroxyalkyl)pyrrole derivative gives a pure 3-acylpyrrole derivative which is difficult to obtain by direct substitution in the pyrrole ring. Acylation of pyrrole yields 1- and/or 2-acetylpyrrole, whereas acylation of 1-methylpyrrole forms both 2- and 3-acetyl-1-methylpyrrole, the latter in smaller amount.[3] When a similar procedure was used, 3-(1-hydroxyethyl)-1-methylpyrrole was converted to 3-acetyl-1-methylpyrrole in 76% yield.[4] Recently the decarbonylation of 1-methyl-4-acetyl-2-pyrrolaldehyde was used as a method to prepare 3-acetyl-1-methylpyrrole.[8]

1. Department of Chemistry, Boston University, Boston, MA 02215 (H. M. G. on leave from Southwestern at Memphis, Memphis, TN 38112). This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.
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8. Private communcation with Professor H. J. Anderson.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-(1-Hydroxybutyl)-1-methylpyrrole: 1 H-Pyrrole-3-methanol, 1-methyl-α-propyl- (10); 70702-66-8

3-Butyroyl-1-methylpyrrole: 1-Butanone, 1-(1-methyl-1 H-pyrrol-3-yl)- (10); 62128-46-5

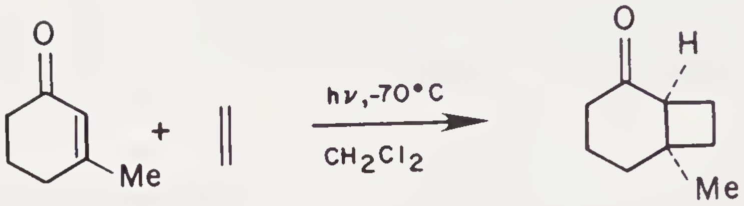
1-Methylpyrrole: Pyrrole, 1-methyl- (8); 1 H-Pyrrole, 1-methyl- (9); 96-54-8

Butyraldehyde (8); Butanal (9); 123-72-8

PHOTOCYCLIZATION OF AN ENONE TO AN ALKENE:

6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE

(Bicyclo[4.2.0]octan-2-one, 6-methyl-)



Submitted by R. L. Cargill,[1a] J. R. Dalton, G. H. Morton, and W. E. Caldwell[1].
Checked by Barry A. Wexler, Amos B. Smith, III, and Carl R. Johnson.

1. Procedure

The irradiation apparatus (Note 1) is charged with a solution of 25.0 g (0.277 mol) of 3-methyl-2-cyclohexenone (Note 2) in reagent grade dichloromethane (Note 3). A gas outlet tube to an efficient hood is placed in one 14/20 standard taper joint; in the other, there is a stopper which can be removed for periodic sampling. The cooling water is turned on (Note 4) and the apparatus is immersed in a dry ice/2-propanol bath while the chilled solution is saturated with ethylene (Note 5). The lamp is inserted into the well and turned on (Note 6). Progress of the irradiation is conveniently followed by gas chromatography (Note 7). After ca. 8 hr, most of the starting material has reacted. At this time, the lamp is turned off and the apparatus removed from the cooling bath. The reaction mixture is degassed with a slow stream of nitrogen while it warms to room temperature, dried over magnesium sulfate, and concentrated with a rotary evaporator at a temperature below 30°C (Note 8). The product is isolated by distillation to afford 27-28 g (86-90%) of 6-methylbicyclo[4.2.0]octan-2-one, bp 62-65°C (3.5 mm) (Notes 9 and 10).

2. Notes

1. The apparatus is similar to one described earlier.[2] A triple-walled Dewar is constructed of Pyrex according to Figure 1. For further discussion concerning this immersion well contact Joel M. Babbitt, Glassblower, Department of Chemistry, University of South Carolina, Columbia, SC 29208. The evacuated jacket permits the safe use of circulating tap water as a lamp coolant even when irradiations are conducted in a dry-ice bath. A further advantage is that three layers of Pyrex constitute an effective filter for light in the 280-300 nm region so that secondary photolysis of cycloadducts is not usually observed. The irradiation flask is a cylindrical vessel of suitable volume fitted with a coarse, fritted disc for gas dispersion and a flanged lip. The light source is either a G.E. H1000-A36-15, Westinghouse H-36GV-1000, or equivalent lamp with the outer globe removed, used in conjunction with a G.E 35-9627-6009 ballast. These lamps are available from the General Electric Company, Lamp Division, Charlotte, North Carolina.

2. This material can be purchased from Aldrich Chemical Co. or it can be prepared from Hagemann's ester.[3]

3. The volume of solution will vary depending on the exact volume of the apparatus, the temperature, and the miscibility of gaseous reactant in the solvent. The solution should completely surround the lamp, but should not overflow the vessel. The submitters used a volume of 1100 mL and the checkers used 200 mL.

4. If the flow of cooling water is stopped while the apparatus is cold, the water may freeze and crack the immersion well. The vacuum jacket provides greater insurance against this problem than is available in the commercially available wells used with the usual 450 watt lamps.[2]

5. CP grade ethylene (Matheson) was used without purification. A flow of ca. 100 mL/min of ethylene for 2-3 hr is adequate for saturation. Gas flow is continued throughout the irradiation in order to maintain a high concentration of ethylene and for stirring.

6. The lamp will not start if it is too cold or too hot. The practice of blowing nitrogen over the lamp to remove ozone is not recommended as this cools the lamp and decreases its output significantly, resulting in an unnecessarily long irradiation period.

7. The submitters used a Varian 1200 FID chromatograph with a 7% Carbowax 20 M on Chromosorb Q, 8-ft x 0.125-in column, a carrier gas (N_2) flow rate of 40 mL/min, column 160°C, injector 220°C, detector 215°C. Retention times were 3-methyl-2-cyclohexenone, 4.2 min, and 6-methylbicyclo[4.2.0]octan-2-one, 3.9 min, respectively.

8. If the solvent is removed without care a considerable amount of volatile product may be lost.

9. This material is contaminated with ~ 10% of 3-methylcyclohexenone. Material of greater purity can be obtained by extending the time of irradiation, by carrying out an efficient distillation of product, or by decomposing starting material with potassium permanganate prior to distillation.

10. The product has the following spectral properties: IR (CCl_4) cm^{-1}: 1700; ^1H NMR (CCl_4) δ: 1.21 (s, 3 H, methyl), 1.9 (m, 11 H, all other protons); ^{13}C NMR (C_6D_6) δ (based on δ C_6D_6 128.00): 211.63, 51.34, 40.86, 39.45, 35.26, 31.20, 28.84, 21.45, 20.35; ms (m/e) 138.1041 (parent ion).

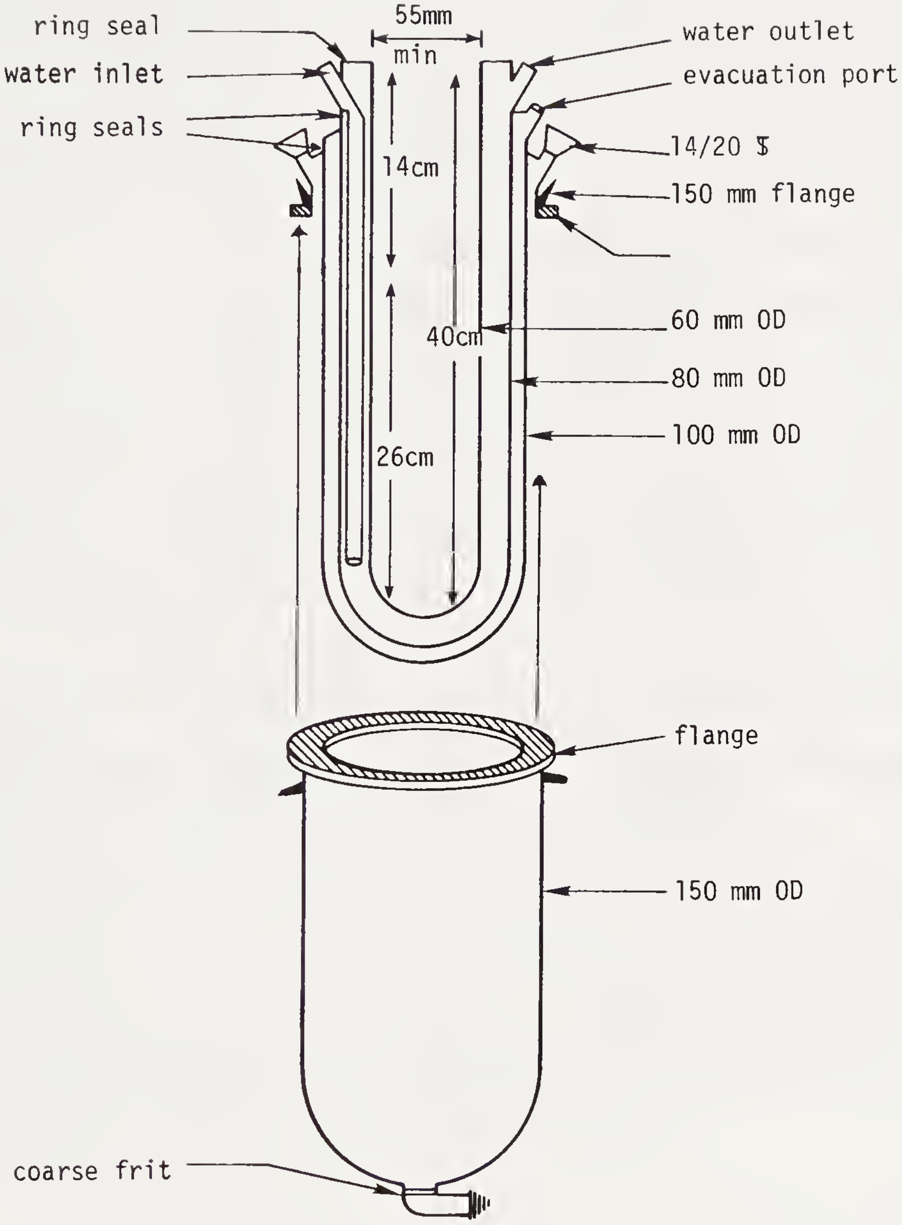


Figure. Irradiation Vessel

3. Discussion

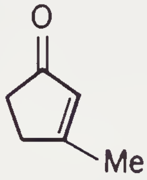
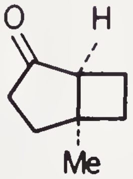
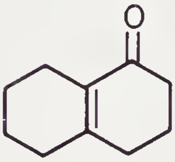
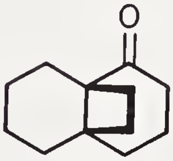
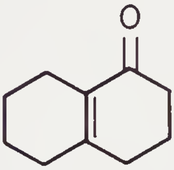
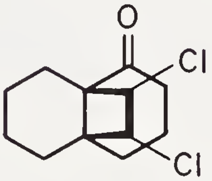
Although photochemical cycloadditions have gained acceptance in synthetic chemistry,[4] most such reactions are limited to a relatively small scale. The use of a 1000-watt street lamp permits the irradiation of up to 1 mol of substrate in less time than 0.2 mol can be irradiated with the conventional 450-watt lamps. Thus, under optimum conditions, the submitters were able to add ethylene to 3-methylcyclohexenone on a 20-g scale in 48 hr (80%) with a 450-watt lamp; with the apparatus described here 94 g of this enone was condensed with ethylene in 8 hr (91%).

Some general points regarding photochemical cycloadditions deserve mention. (1) Since the reaction is first order in olefin, the concentration of olefin (especially gaseous olefins) is of critical importance; therefore, the cycloadditions are carried out at low temperature. In some cases, however, low temperature can be detrimental.[5] (2) Since lamp output deteriorates with lamp age, the rates of otherwise identical cycloadditions are unlikely to be the same; therefore, it is of critical importance that the progress of each photochemical reaction be followed by some suitable means (GLC, IR, UV, NMR, etc). (3) As long as all the incident light of appropriate wavelength is absorbed by the enone the reaction proceeds at a rate independent of enone concentration; thus, the highest concentration of enone at which dimerization can be avoided is optimal.

Several examples of preparative cycloadditions are listed in Table I.

TABLE I

PREPARATIVE-SCALE CYCLOADDITIONS

Entry	Enone	Weight (g)	Olefin	Time (hr)	Product(s)	Yield (%)
1.		25	C_2H_4	12		90 (ref 6)
2.		10	C_2H_4	6		71 (ref 7)
3.		20	ClHC=CHCl	10		93[a] (ref 8)

---

[a] A mixture of cis and trans olefins was used; a mixture of diastereomeric products was obtained. Both olefins give similar mixtures.

1. Department of Chemistry, University of South Carolina, Columbia, SC 29208. a) Present address: Cargill Interests, Ltd., P.O. Box 992, Longview, TX 75606.
2. Bloomfield, J. J.; Owsley, D. C. *Org. Photochem. Synth.* **1976**, *2*, 36.
3. Smith, L. I.; Rouault, G. F. *J. Am. Chem. Soc.* **1943**, *65*, 631.
4. For reviews see: Eaton, P. E. *Acct. Chem. Res.* **1968**, *1*, 50; de Mayo, P. *Acct. Chem. Res.* **1971**, *4*, 41; Bauslaugh, P. G. *Synthesis* **1970**, 287; Sammes, P. G. *Synthesis* **1970**, 636; Dilling, W. L. *Chem. Rev.* **1966**, *66*, 373; **1969**, *69*, 845; Wiesner, K. *Tetrahedron* **1975**, *31*, 1655; Dilling, W. L. *Photochem. Photobiol.* **1977**, *25*, 605; 1977, *26*, 557.
5. Loutfy, R. O.; de Mayo, P. *J Am. Chem. Soc.* **1977**, *99*, 3559.
6. Cargill, R. L.; Wright, B. W. *J Org. Chem.* **1975**, *40*, 120.
7. Peet, N. P.; Cargill, R. L.; Bushey, D. F. *J. Org. Chem.* **1973**, *38*, 1218.
8. Rae, I. D.; Umbrasas, B. N. *Aust. J. Chem.* **1975**, *28*, 2669

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6-Methylbicyclo[4.2.0]octan-2-one: Bicyclo[4.2.0]octan-2-one, 6-methyl- (8,9); (13404-66-5)

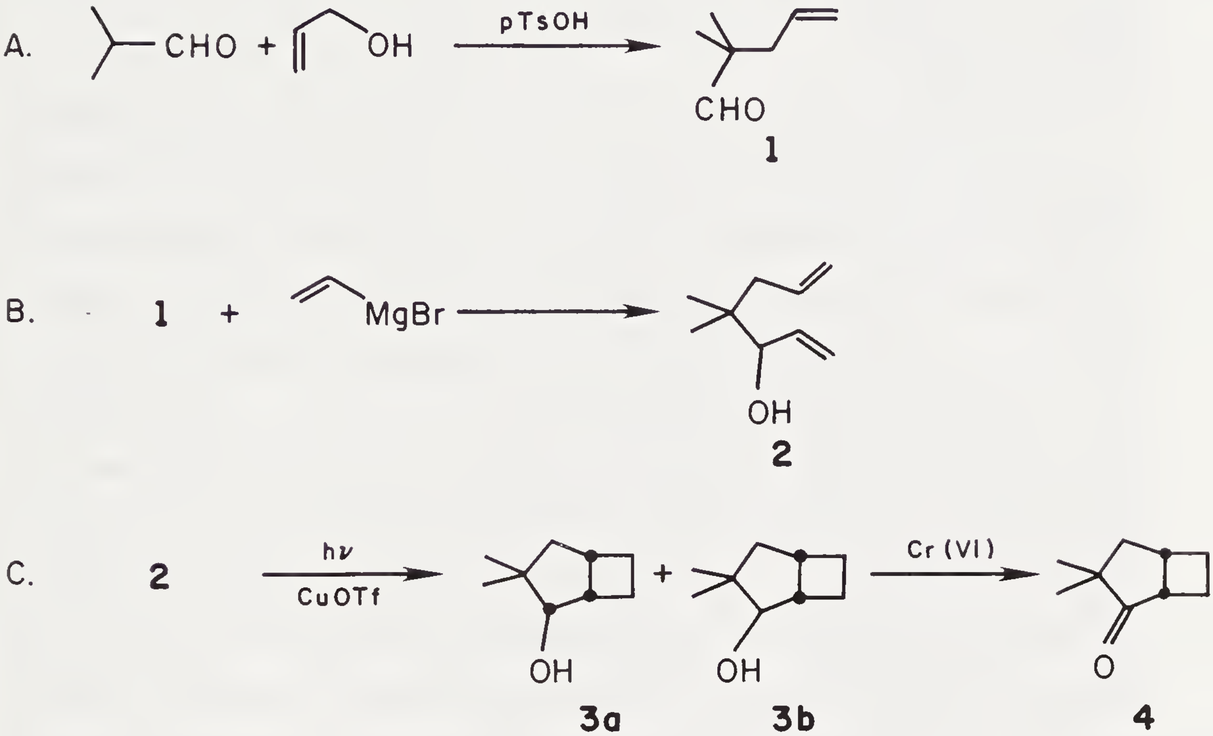
3-Methyl-2-cyclohexenone: 2-Cyclohexen-1-one, 3-methyl- (8,9); (1193-18-6)

Ethylene (8); Ethene (9); (74-85-1)

COPPER (I)-CATALYZED PHOTOCYCLOADDITION:

3,3-DIMETHYL-cis-BICYCLO[3.2.0]HEPTAN-2-ONE

(Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl-)



Submitted by Robert G. Salomon and Subrata Ghosh[1].

Checked by Daniel K. Jackson and Richard E. Benson.

1. Procedure

A. 2,2-Dimethyl-4-pentenal. In a 500-mL, one-necked, round-bottomed flask which contains a magnetic stirring bar are placed 108 g (1.5 mol) of isobutyraldehyde (Note 1), 58 g (1.0 mol) of allyl alcohol (Note 1), 230 mL of p-cymene (Note 1), and 0.4 g (2 mmol) of p-toluenesulfonic acid monohydrate

(Note 1). The mixture is heated with a mantle with stirring for 32 hr under a 50-cm fractionating column packed with 6-mm glass beads and topped by a Dean-Stark trap. The reaction mixture is then distilled through the packed column. The fraction which boils at 120°-126°C is collected. The yield is 86.0-87.3 g (77-78%) of 2,2-dimethyl-4-pentenal (**1**) as a clear, colorless oil, n_D^{25} 1.4216 (Note 2).

B. 4,4-Dimethyl-1,6-heptadien-3-ol. In a 1-L, three-necked, round-bottomed flask, fitted with mechanical stirrer, 500-mL pressure-equalizing addition funnel, and condenser topped with a gas inlet for maintaining an atmosphere of dry nitrogen, is placed 17 g (0.7 g-atom) of magnesium turnings (Note 3). The system is flushed with nitrogen, and methanol maintained at -20°C is circulated through the condenser (Note 4). From a solution of 70 g (0.65 mol) of vinyl bromide (Note 5) in 400 mL of tetrahydrofuran (Note 6), a 50-mL quantity is added by means of the addition funnel, and the resulting mixture is stirred mechanically. After a few minutes an exothermic reaction ensues which subsides after several minutes of vigorous boiling (Note 7). The remainder of the vinyl bromide solution is added at such a rate as to maintain a gentle reflux. After stirring at room temperature for 12 hr, the resulting mixture is cooled with an ice-water bath, and 62 g (0.55 mol) of 2,2-dimethyl-4-pentenal (**1**) is added dropwise over 25-30 min through the addition funnel which is then rinsed with 10 mL of dry tetrahydrofuran. The resulting mixture is stirred for 1 hr at 23°C and then poured into a mixture of 1 kg of ice, 200 mL of concd hydrochloric acid, and 400 mL of water. The resulting mixture is extracted with three 500-mL portions of ether. The combined extracts are washed successively with 400 mL of water, 400 mL of saturated aqueous sodium bicarbonate, and 400 mL of saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the ether is removed with a rotary evaporator. Distillation of the product through a 15-cm vacuum-jacketed Vigreux column gives 63.4-63.8 g (82-83% yield) of 4,4-dimethyl-1,6-heptadien-3-ol (**2**), bp 76-79°C (20 mm), n_D^{24} 1.4562 (Note 8).

C. 3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-ol. A 25-mL test tube is charged with 0.3-0.4 g (0.6-0.8 mmol) of bis(copper trifluoromethanesulfonate)benzene complex (Note 9) and sealed with a rubber septum under an atmosphere of dry nitrogen. A solution of 5 mL (4.3 g, 0.031 mol) of 4,4-dimethyl-1,6-heptadien-3-ol in 10 mL of ether (Note 10) is added by means of a syringe. The resulting solution is poured (Note 11) into a nitrogen-flushed Pyrex 250-mL annular reactor fitted with a magnetic stirrer, an internal concentric water-jacketed quartz immersion well, and a water-cooled reflux condenser topped with a gas inlet for maintaining an atmosphere of dry nitrogen. An additional 20 mL (17.4 g, 0.124 mol) of the hydroxydiene 2 in 200 mL of dry ether is added. The resulting solution is stirred and irradiated for 15 hr with a 450-watt medium pressure Hanovia mercury arc (Note 12) which is suspended in the immersion well. At the end of that time an opaque film of copper is wiped from the immersion well, and irradiation is then continued for an additional 7 hr. The resulting solution is shaken in a separatory funnel with a mixture of 100 g of ice and 100 mL of concd aqueous ammonium hydroxide. The organic phase is separated and the aqueous phase is extracted with 100 mL of ether. The organic phases are combined and washed with 100 mL of saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 19.0-19.9 g (88-92% yield) of 3,3-dimethyl-cis-bicyclo[3.2.0]heptan-2-ol (**3**), bp 80-84°C (12 mm), n_D^{25} 1.4761-1.4783 (Note 13).

D. 3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-one. In a 500-mL Erlenmeyer flask which contains a magnetic stirring bar is placed 35.1 g (0.25 mol) of 3,3-dimethyl-cis-2-bicyclo[3.2.0]heptanol and 200 mL of acetone (Note 14). The solution is cooled with an ice-water bath while 100 mL of 2.7 M Jones reagent (Note 15) is added in small portions over 15 min with vigorous stirring (Note 16). The ice-water bath is removed and the reaction mixture is stirred at 5-20°C for 2 hr. Then 400 mL of saturated aqueous sodium chloride is added, and the resulting mixture is extracted with three 500-mL portions of ether. The extractions are combined and washed successively with 400 mL of saturated aqueous sodium chloride and 200 mL of saturated aqueous sodium bicarbonate. The solvent is removed by means of a rotary evaporator and the resulting product is transferred to a separatory funnel and separated from the water. The aqueous layer is extracted with 50 mL of ether. The product and the ether layer are combined and dried over anhydrous sodium sulfate. The ether is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 28.7-32.2 g (83-93% yield) of 3,3-dimethyl-cis-bicyclo[3.2.0]heptan-2-one (**4**), bp 72-75°C (12 mm), n_D^{20} 1.4622 (Note 17).

2. Notes

1. Isobutyraldehyde, allyl alcohol, p-cymene, and p-toluenesulfonic acid monohydrate were purchased from Aldrich Chemical Company, Inc., and used as received.

2. The submitters state that the distilled product was about 97% pure as shown by GLC analysis on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh and operated at 140°C. The retention time is about

1.40 min. Two minor impurities with retention times of about 0.95 and 1.15 min were detected, in roughly equal amounts. The product has the following spectral properties: IR (neat) cm^{-1}: 2965 (m), 2925 (m), 1725 (vs), 1465 (m), and 915 (m), together with numerous weaker absorption bands; ^1H NMR ($CDCl_3$) δ: 1.04 (s, 6 H), 2.22 (d, 2 H, J = 7.0), 4.9-5.3 (m, 2 H), 5.4-6.2 (m, 1 H), 9.40 (s, 1 H).

3. Reagent available from Fisher Scientific Company was used.

4. A Neslab ULT-80 refrigerated circulating bath was used. Alternatively, a Dewar condenser cooled with acetone-dry ice can be used.

5. Vinyl bromide, available from Aldrich Chemical Company Inc., was used as received.

6. Tetrahydrofuran, anhydrous, 99.9% (water content <0.006%) was purchased from Aldrich Chemical Company, Inc., and used as received. The vinyl bromide solution was prepared in a 500-mL, round-bottomed flask fitted with a glass stopper. The stoppered flask containing the tetrahydrofuran was chilled to about 5°C and weighed, The vinyl bromide, also chilled to about 5°C, was rapidly poured into the tetrahydrofuran until the desired amount had been added. The flask was stoppered, the contents mixed by shaking, allowed to warm to about 16°C, and then added to the pressure-equalizing addition funnel.

7. The checkers found it necessary to initiate the reaction with a crystal of iodine.

8. The submitters state that the purity of the product is greater than 98% by gas chromatographic analysis on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh and operated at 140°C. The retention time is about 4.7 min. An impurity with a retention time of about 2.9 min was detected. The product has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 0.84 (s, 3 H), 0.88, (s, 3 H), 1.80-2.30 (m, 2 H), 2.69 (s, 1 H), 3.78 (d, 1 H, J = 6), 4.87-5.33 (m, 4 H), 5.57-6.13 (m, 2 H).

9. The copper complex is available from Strem Chemicals, Inc., under the name cuprous triflate (benzene complex). The checkers recommend handling the material in a dry box because of its high moisture and air sensitivity.

10. Anhydrous ether was distilled from lithium aluminum hydride under dry nitrogen immediately before use.

11. The submitters state that the copper(I) triflate is quite air stable in solution in the presence of the allylic alcohol.

12. The checkers recommend the use of a relatively new arc lamp. Substantially higher conversions were obtained with a new lamp because of an apparent bathochromic shift in the frequency of the light emitted as the lamp ages, thus lessening the intensity of light in the important absorption region for the reaction.

13. The submitters state that the purity of the product is greater than 97% by GLC analysis on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh and operated at 140°C. The retention time is about 8.0 min. The only impurity is unreacted diene with a retention time of about 4.7 min. The product is an epimeric mixture. TLC analysis by the submitters on 0.25-mm silica gel with 20% ethyl acetate in hexane shows major (>90%) and minor (<10%) epimers with R_f values of 0.32 and 0.23 respectively. The epimers are separable by column chromatography on silica gel with ethyl acetate-hexane mixtures as eluting solvents. A 3.1-g portion of the distilled isomer mixture was chromatographed by the checkers on 475 g of silica gel (Silica Woelm TSC - activity III/30 mm) using 5% ethyl acetate/hexane as eluent. The elution proceeded as follows: 1520 mL, nil; 1440 mL, 2.7 g of endo isomer; 1400 mL, nil; 2010 mL, 0.20 g of exo isomer. Analysis of the ^1H NMR spectrum of the distilled product confirms that the reaction is greater than 90% stereoselective in favor of the endo epimer. The major epimer, 3,3-

dimethyl-endo-cis-bicyclo[3.2.0]heptan-2-ol, has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 0.81 (s, 3 H), 1.13 (s, 3 H), 1.4-3.2 (m, 9 H), 3.66 (d, 1 H), J = 6.7); ^{13}CMR ($CDCl_3$) δ: 16.3 (t), 22.5 (q, CH_3), 26.0 (t), 27.8 (q, CH_3), 36.0 (d), 42.8 (d), 45.5 (t), 45.8 (s, C-3), 80.9 (d, C-2). The minor epimer, 3,3-dimethyl-exo-cis-bicyclo[3.2.0]heptan-2-ol, has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 0.77 (s, 3 H), 1.08 (s, 3 H), 1.2-2.9 (m, 9 H), 3.80 (d, 1 H, J = 4.6); ^{13}CMR ($CDCl_3$) δ 20.7 (q, CH_3), 24.0 (t), 26.5 (q, CH_3), 27.1 (t), 34.6 (d), 45.6 (s, C-3), 45.8 (d), 46.7 (t), 88.7 (d, C-2).

14. Certified ACS grade acetone purchased from Fisher Scientific Company was used as received.

15. Eisenbraun, E. J. *Org. Synth. Coll. Vol. V* **1973**, 310-314.

16. Initially a gummy green precipitate is formed which is difficult to stir magnetically. Eventually, however, the inorganic by-products become more fluid. The use of a mechanical stirrer may be desirable.

17. The submitters state that the distilled product is <98% pure by GLC on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh, operated at 140°C. The relative retention time is 2.3 versus an unidentified impurity at 1.0. The distilled product has the following spectral properties: IR (neat) cm^{-1}: 2960 (vs), 2940 (vs) and 1735 (vs) and other weaker bands. ^{1}H NMR (CCl_4) δ: 0.92 (s, 3 H), 1.12 (s, 3 H), 1.4-3.0 (m, 8 H); ^{13}CMR ($CDCl_3$), δ: 22.7, 24.1, 25.6, 26.4, 31.0, 43.9, 44.2, 48.4, 224.7.

3. Discussion

This procedure illustrates a general method for the preparation of 2-hydroxybicyclo[3.2.0]heptanes by copper(I)-catalyzed photobicyclization of 3-hydroxy-1,6-heptadienes,[2] and a general route to the requisite dienes from allyl alcohols by conversion to 4-pentenals and treatment of the latter with vinyl Grignard reagents.

Compound 1, 2,2-dimethyl-4-pentenal, has been prepared by the Claisen rearrangement route[3] described above and by reaction of isobutyraldehyde with allyl chloride in the presence of aqueous sodium hydroxide and a phase-transfer catalyst.[4] Both routes are applicable to the synthesis of a variety of substituted 4-pentenals.

cis-Bicyclo[3.2.0]heptan-2-ols have been prepared by reduction[5] of the corresponding cis-bicyclo[3.2.0]-heptan-2-ones which have been prepared by photocycloaddition of alkenes with 2-cyclopentenones.[6] The synthetic strategy of the present procedure is complementary.

1. Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106.
2. Salomon, R. G.; Coughlin, D. J.; Easler, E. M. *J. Am. Chem. Soc.* **1979**, *101*, 3961-3963.
3. Brannock, K. C. *J. Am. Chem. Soc.* **1959**, *81*, 3379-3383.
4. Dietl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 1273-1275.
5. Svensson, T. *Chem. Scr.* **1973**, *3*, 171-175.
6. For reviews, see the following. Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50-57; Bauslaugh, P. G. *Synthesis* **1970**, 287-300; de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41-47.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Numbers)

4-Pentenal, 2,2-dimethyl- (8,9); (5497-67-6)

p-Cymene (8); Benzene, 1-methyl-4-(1-methylethyl)- (9); (99-87-6)

1,6-Heptadien-3-ol, 4,4-dimethyl- (9); (58144-16-4)

Ethylene, bromo-(8); Ethene, bromo- (9); (593-60-2)

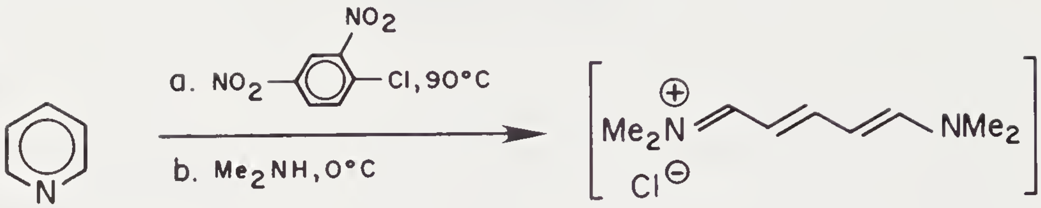
Bicyclo[3.2.0]heptan-2-ol, 3,3-dimethyl- (9); (71221-67-5)

Bis(copper(I) trifluoromethanesulfonate)benzene complex: Copper, (μ-(benzene))bis(trifluoromethanesulfonato-O)di- (9); (37234-97-2

Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl- (9); (71221-70-0)

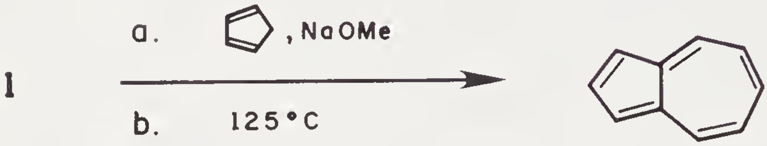
SYNTHESIS OF AZULENE

A.



1

B.



Submitted by Klaus Hafner and Klaus-Peter Meinhardt[1].

Checked by Stephen G. Senderoff and Andrew S. Kende.

1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, thermometer, and reflux condenser provided with a calcium chloride drying tube is charged with 202.6 g (1.0 mol) of 1-chloro-2,4-dinitrobenzene (Note 1) and 1.2 L of dry pyridine (Note 2). The mixture is heated while it is stirred in a water bath to 80-90°C for 4 hr, during which time a thick yellow precipitate of N-(2,4-dinitrophenyl)pyridinium chloride is formed (Note 3). After cooling to 0°C a solution of 100.0 g (2.22 mol) of dimethylamine in 300 mL of dry pyridine was pre-chilled to 0°C and added dropwise over a period of about 30 min with stirring. The resulting brownish-red liquid reaction mixture is allowed to warm to room temperature and stirring is continued for 12 hr. The drying tube is replaced by a gas inlet and the system is flushed with dry nitrogen in a hood. Under nitrogen, 70.0 g (1.06 mol) of ice-cold, freshly-distilled cyclopentadiene (Note 4) is added, and subsequently 400 mL of 2.5 M sodium methoxide solution (Note 5) is slowly added dropwise to the stirred reaction mixture. During addition of the sodium methoxide, the temperature rises to 35-40°C. After the addition is completed, stirring is continued for another 4 hr. The reaction vessel is immersed in an oil bath, the dropping funnel removed, and the flask is fitted with a distillation head. The stirred mixture is cautiously heated under nitrogen (Note 6), and a mixture of pyridine and methanol is distilled off until the temperature of the reaction mixture has increased to 105-110°C (Note 7). After the distillation head is removed and 1 L of dry pyridine is added, the black mixture is heated with stirring under a nitrogen atmosphere for 4 days with a bath temperature of 125°C. It is then cooled to 60°C, the reflux condenser is replaced by a distillation head, and pyridine is removed under reduced pressure (Note 8). The gummy black solid residue is removed by a spatula and rinsed with hexanes. It is extracted in a Soxhlet apparatus with 1.5 L of hexanes in several batches. To remove the remaining pyridine, the combined blue hexane rinse and the extraction solutions are carefully washed with two 150-mL portions of 10% aqueous hydrochloric acid, then water (Note 9). The organic layer is dried with anhydrous sodium sulfate, the drying agent is removed by filtration, and the solvent is distilled through a 50-cm vacuum-jacketed Vigreux column. The crude azulene is purified by chromatography on activity II alumina (Note 10) with hexane, and yields azulene as blue plates, mp 96-97°C, yield 65-75 g (51-59%) (Note 11).

2. Notes

1. Commercial 1-chloro-2,4-dinitrobenzene was obtained from Aldrich Chemical Company, Inc. (Milwaukee) or from Bayer, AG (Leverkusen, FRG) and used directly.

2. Commercial pyridine was dried over potassium hydroxide or calcium hydride and distilled prior to use. The checkers used reagent grade pyridine (Mallinckrodt AR) which was distilled from KOH and stored over Linde 4Å Molecular Sieves.

3. The reaction mixture should be evenly warmed to 80-90°C within 30 min with efficient mechanical stirring to prevent caking or "hot spots".

4. Dicyclopentadiene, obtained from the Aldrich Chemical Company, Inc. (or E. Merck, Darmstadt, FRG), was cracked just prior to use according to the procedure of Fieser and Williamson,[2] to give the monomer, bp 40-42°C.

5. Sodium methoxide was prepared just prior to use from 23.0 g (1.0 g-atom) of sodium metal and 400 mL of anhydrous methanol (distilled from magnesium turnings), then cooled to room temperature.

6. *Caution!* Dimethylamine is evolved.

7. Approximately 600 mL of distillate will be collected.

8. The blue pyridine distillate is redistilled through a 50-cm vacuum-jacketed Vigreux column (to avoid loss of azulene) until approximately 1.7 L is collected; the residual azulene is combined with the main residues for extraction.

9. A total volume of 2 L of hexane washes results, accompanied by the gradual precipitation of a yellow solid from the hexane washes. The acid-wash procedure frequently leads to emulsions and gummy yellow solid in both phases; back-extraction of the "aqueous" layer with hexane may be necessary.

10. Alumina was purchased from Macherey, Nagel and Co., Düren (FRG). The checkers employed 650 g of neutral alumina (Fisher, adsorption grade, 80-200 mesh) packed in a 40-cm high column. Yellow impurities remained on the column, while the blue azulene came off with the hexane solvent front.

11. Further purification of azulene may be achieved by sublimation at reduced pressure, mp 99°C.[3] The checkers found that mechanical losses, particularly as mentioned in Note 9, lead to reduction in yield with reduction in scale (0.1 mol, 39% yield; 0.5 mol, 43% yield; 0.8 mol, 79% yield).

3. Discussion

Azulene has been synthesized by a variety of methods: by dehydrogenation of hydroazulenes,[3] by annelation of a 7-membered ring on a 5-membered ring either by ring-closure of vinylogous aminopentafulvenes,[4,5] or by cycloadditions of aminopentafulvenes with activated 1,3-dienes or alkynes,[6] and by annelation of a 5-membered ring on a 7-membered ring starting from troponoids or heptafulvenes.[7,3b] Of these, the Ziegler-Hafner synthesis of azulene[4] by thermal cyclization of the 6-(4-methylanilino-1,3-butadienyl)pentafulvene proved to be the most versatile. Azulene is also simply prepared from 6-dimethylaminopentafulvene and thiophene 1,1-dioxide or from 6-acyloxypentafulvenes and 1-diethylaminobutadiene, but with lower yields.[6b,d,e]

The present procedure, based on the Ziegler-Hafner synthesis, is simple and avoids the use of benzidine for the ring-closure of the pentafulvene and isolation of the 5-dimethylamino-2,4-pentadienylidenedimethyliminium perchlorate.[8] Other amines were also checked; with N-methylaniline ring-closure of the resulting pentafulvene in pyridine failed; with diethylamine a delay in boiling can take place during the reaction.

Substituted azulenes can be prepared in the same manner by the use of substituted cyclopentadienes or substituted pentamethinium salts.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

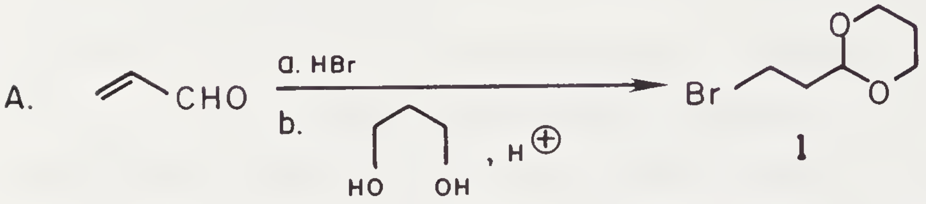
Azulene (8,9); (275-51-4)

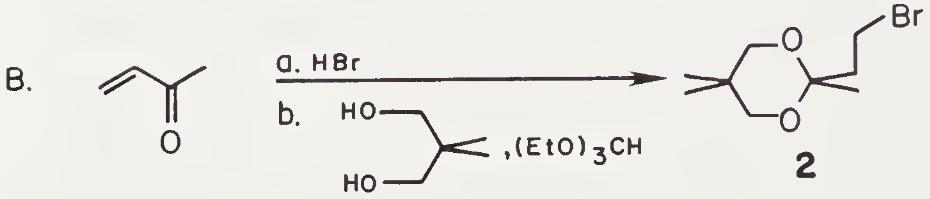
1-Chloro-2,4-dinitrobenzene: Benzene, 1-chloro-2,4-dinitro- (8,9); (97-00-7)

Dimethylamine (8); Methanamine, N-methyl- (9); (124-40-3)

Dicyclopentadiene: 4,7-Methanoindene, 3a,4,7,7a-tetrahydro- (8); 4,7-Methano-1-H-indene, 3a,4,7,7a-tetrahydro- (9); (77-73-6)

β-HALOACETALS AND -KETALS: 2-(2-BROMOETHYL)-1,3-DIOXANE AND 2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE





Submitted by J. C. Stowell, D. R. Keith, and B. T. King[1].

Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. 2-(2-Bromoethyl)-1,3-dioxane (**1**). A 2-L, three-necked flask is equipped with a mechanical stirrer, thermometer, and gas inlet tube. In the flask are placed 750 mL of dichloromethane, 112 g (2.00 mol) of acrolein (Note 1), and 0.10 g of dicinnamalacetone indicator (Note 2) under nitrogen. The yellow solution is cooled to 0-5°C with an ice bath. Gaseous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator becomes deep red (Note 4). The ice bath is removed and 1.0 g of p-toluenesulfonic acid monohydrate and 152.2 g (2.00 mol, 144 mL) of 1,3-propanediol (Note 1) are added. The yellow solution is stirred at room temperature for 8 hr, and then concentrated with a rotary evaporator. The residual oil is washed with two 250-mL portions of saturated aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Vacuum distillation through a 30-cm Vigreux column yields 252 g (65%) of **1** as a colorless liquid, bp 72-75°C (2.0 mm), n_D^{20} 1.4809 (Note 5).

B. 2,5,5-Trimethyl-2-(2-bromoethyl)-1,3-dioxane (2). A 1-L, three-necked flask is equipped with a magnetic stirrer and a gas inlet tube. In the flask are placed 700 mL of dichloromethane, 140 g (2.00 mol) of methyl vinyl ketone (Note 6), and 0.010 g of dicinnamalacetone indicator (Note 2). Anhydrous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator changes to deep red (Note 7). The gas inlet tube is removed and 208 g (2.00 mol) of neopentanediol, 296 g (2.00 mol) of triethyl orthoformate, and 0.67 g of p-toluenesulfonic acid monohydrate are added to the solution. The flask is stoppered and stirred at room temperature for 1-2 hr and then concentrated by rotary evaporation (Note 8). The concentrated solution is washed twice with saturated sodium bicarbonate solution (*Caution*: there is some foaming). The bicarbonate washes are extracted three times with dichloromethane and the combined organic portions dried over anhydrous K_2CO_3. Rotary evaporation followed by vacuum distillation of the residue through a 30-cm Vigreux column yields 256 g (54%) of **2** as a clear, colorless oil, bp 65°C (0.3 mm), n_D^{22} 1.4687 (Note 9).

2. Notes

1. The acrolein, 1,3-propanediol, and cinnamaldehyde were purchased from Aldrich Chemical Company, Inc.

2. The indicator was prepared by the method of Diehl and Einhorn.[2] A solution of 5 g of sodium hydroxide in 50 mL of water and 40 mL of ethanol is prepared in a 250-mL Erlenmeyer flask. To this is added a solution of 1.84 mL (0.025 mol, 1.45 g) of acetone in 6.3 mL (0.050 mol, 6.6 g) of freshly distilled cinnamaldehyde (Note 1). This mixture is stirred thoroughly at room temperature for 30 min. The resulting voluminous yellow precipitate is filtered with suction, washed with 100 mL of water, and dried, affording 6.5 g of 1,9-diphenylnona-1,3,6,8-tetraen-5-one. Recrystallization from 200 mL of hot 95% ethanol gives 3.5 g of yellow crystals, mp 142-143°C (lit[2] mp 142°C). This indicator is also available from Aldrich Chemical Co.

3. The anhydrous hydrogen bromide was purchased in a lecture bottle from Matheson. A trap is used between the lecture bottle and the gas inlet tube.

4. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 3-bromopropanal (60 MHz, CH_2Cl_2) δ: 3.04 (t, 2 H), 3.59 (t, 2 H), 10.67 (s, 1 H).

5. Product 1 has the following spectral characteristics: IR (neat) cm^{-1}: 2980, 2870, 1250, 1150, 1140, 1015; ^1H NMR (90 MHz, $CDCl_3$) δ: 1.38 (d of m, 1 H, one 5-position on dioxane ring), 1.8-2.4 (m, the other 5-position on the dioxane ring), 2.14 (d of t, 2 H, CH_2-C-Br), 3.45 (t, 2 H, CH_2Br), 3.80 (d of t, 2, 4, and 6-positions on ring), 4.15 (d of double d, 2, 4, and 6-positions on ring), 4.71 (t, 1 H, 2-position on ring; ^{13}C magnetic resonance (22.5 MHz, $CDCl_3$) δ: 100.06, 66.86, 38.08, 27.79, 25.79.

6. The neopentanediol and triethyl orthoformate were purchased from Aldrich Chemical Co., Inc. and used as received. Failure to distil the methyl vinyl ketone, also obtained from Aldrich Chemical Co., to a clear, colorless liquid before use resulted in difficulty in determining the endpoint of the reaction with HBr. Therefore, the methyl vinyl ketone was distilled prior to use at reduced pressure.

7. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 4-bromo-2-butanone (60 MHz, CH_2Cl_2) δ: 2.15 (s, 3 H, CH_3CO), 3.02 (t, 2 H, CH_2CO), 3.52 (t, 2 H, CH_2Br); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 25.75, 30.11, 45.91, 205.12. Little or no exotherm is noticed during the hydrogen bromide addition.

8. The reaction can be conveniently monitored by TLC using silica plates and eluting with 1:4 ethyl acetate-heptane.

9. Product 2 has the following characteristics: IR (neat liquid) cm^{-1}: 2970, 2880, 1260, 1220, 1125, 1085; ^1H NMR (60 MHz, $CDCl_3$) δ: 0.81 (s, 3 H, 5-methyl), 1.01 (s, 3 H, 5-methyl), 1.34 (s, 3 H, 2-methyl), 2.05-2.45 (m, 2 H, CH_2-C-Br), 3.2-3.8 (m, 6 H, CH_2O and CH_2Br); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 19.64, 22.24, 22.76, 26.99, 29.72, 43.25, 70.23, 98.26.

3. Discussion

Cyclic β-haloacetals and -ketals have been prepared by variations on two basic methods. The most frequently used method involves the combination of an α,β-unsaturated carbonyl compound (acrolein, methyl vinyl ketone, crotonaldehyde, etc.) a diol, and the anhydrous hydrogen halide. All possible sequences of combining these three have been used. In most cases the anhydrous acid was dissolved in the diol and then the carbonyl compound was added slowly.[3-7] Alternatively, the acetals of the α,β-unsaturated carbonyl compounds were prepared and isolated and then the hydrogen halide was added.[8] Finally the hydrogen halide may be added to the α,β-unsaturation followed by acetal formation,[9] and this is the basis of the present procedures.

The second general method is the aluminum halide-catalyzed reaction of acid halides with ethylene to give β-halo ketones which are subsequently converted to ketals.[10,11]

The preparations are much simplified if a stoichiometric amount of hydrogen halide is added using an indicator to determine the end point. We have found that 1,9-diphenylnona-1,3,6,8-tetraen-5-one (dicinnamalacetone)[12] is of appropriate basicity to detect excess anhydrous hydrogen halides in organic solvents including chloroform, dichloromethane, benzene, toluene, acetic acid, and acetone (but not in alcohols). The reaction between the hydrogen halide and the α,β-unsaturated carbonyl compound is fast enough at 0 to 25°C that the end point is readily detected, and the yield-lowering use of excess hydrogen halide or long contact times[13] are avoidable. The intermediate β-halo aldehydes are unstable toward trimerization[14] if they are not diluted by a solvent and therefore should not be isolated but used directly in the next step. β-Bromo ketones darken upon isolation and brief storage so they too should be protected directly.

The conversion of the intermediate bromo aldehyde to the dioxane proceeds readily owing to a favorable equilibrium position. However, the equilibrium for the reaction of the bromo ketone with the diol is unfavorable and requires removal of the by-product, water. This is done under mild conditions using ethyl orthoformate.[15]

We have chosen to use 1,3-diols because the Grignard reagents derived from the 1,3-dioxanes are thermally stable.[16] This contrasts with the use of ethylene glycol where the resulting β-haloalkyl dioxolanes give Grignard reagents which decompose at 25 to 35°C.[17-19] Acyclic acetals give insufficient protection to allow preparation of Grignard reagents.[19] The protection of the ketone with 1,3-propanediol is not readily driven to completion, but with neopentanediol the equilibrium lies further toward ketal formation,[20] giving a better yield of more stable ketal.

β-Haloacetals and -ketals have recently seen wide use as alkylating agents[10,21-24] and in the preparation of Grignard reagents. The Grignard reagents have been alkylated,[25] acylated,[16,26] added to carbonyl groups,[5,18,27-32] and used in Michael additions.[33-35] One example also gives a useful Wittig reagent.[9] Subsequent reactions of these products generally require removal of the acetal and ketal groups to regenerate the carbonyl function. This is readily done with aqueous acid in most cases, but not when aldehydes were protected with 1,3-diols because of the high equilibrium stability of the corresponding dioxanes. This problem is readily overcome by first converting to the dimethyl acetal in methanol and then using aqueous acid hydrolysis, or by using other specialized methods.[9,16]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2-(2-Bromoethyl)-1,3-dioxane: m-Dioxane, 2-(2-bromoethyl)- (8); 1,3-Dioxane, 2-(2-bromoethyl)- (9); (33884-43-4)

Acrolein (8); 2-Propenal (9); (107-02-8)

Dicinnamalacetone: 1,3,6,8-Nonatetraen-5-one, - 1,9-diphenyl (8,9); (622-21-9)

1,3-Propanediol (8,9); (504-63-2)

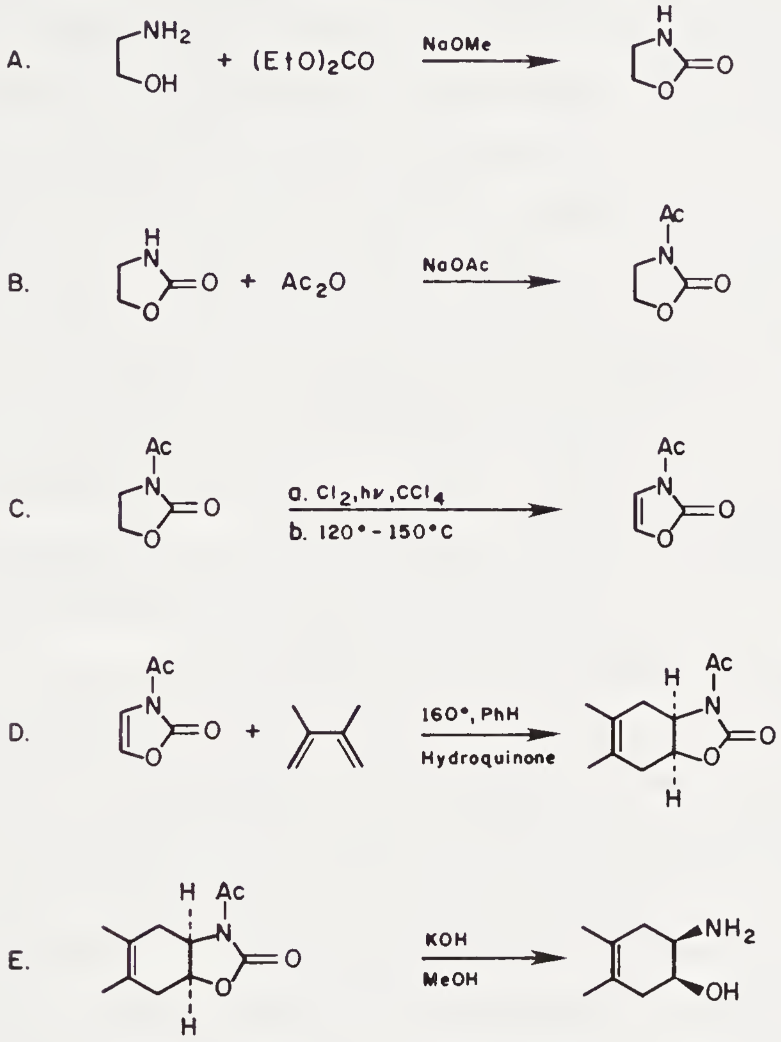
Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

4-Bromo-2-butanone: 2-Butanone, 4-bromo- (8,9); (28509-46-8)

Neopentanediol: 1,3-Propanediol, 2,2-dimethyl- (8,9); (126-30-7)

SYNTHESIS AND DIELS-ALDER REACTIONS OF 3-ACETYL-2(3H)-OXAZOLONE

[2(3H)-Oxazolone, 3-acetyl-]



Submitted by Karl-Heinz Scholz, Hans-Georg Heine, and Willy Hartmann[1].

Checked by Ashok B. Shenvi, Bruce M. Monroe, Richard E. Benson, and Bruce E. Smart

1. **Procedure**

A. 2-Oxazolidinone. A 2-L, three-necked flask equipped with a thermometer, magnetic stirring bar, and a Vigreux column fitted with a distillation head is charged with 305 g (5.0 mol) of freshly distilled 2-aminoethanol, 730 g (6.2 mol) of diethyl carbonate, and 2.5 g (0.05 mol) of sodium methoxide (Note 1). The mixture is stirred and the flask is heated in an oil bath maintained at 125-130°C. Ethanol begins to distill off when the internal temperature reaches 95-100°C. After heating for about 8 hr, the internal temperature reaches 125°C and ethanol ceases to distill (Note 2). The reaction mixture is allowed to cool to 60-70°C and is poured into 1 L of cold chloroform (Note 3). The resulting solution is chilled thoroughly in an ice-water bath and the precipitated product is recovered by filtration. The filtrate is concentrated to 250 mL and chilled to give a second crop. The combined crops are dried in a vacuum oven at 50°C to give 320-339 g (74-78%) of white crystals, mp 86-88°C [lit.[2] mp 87-89°C] (Note 4).

B. 3-Acetyl-2-oxazolidinone. A 3-L, one-necked flask equipped with a reflux condenser and a magnetic stirring bar is charged with 326 g (3.75 mol) of 2-oxazolidinone, 94 g (1.15 mol) of anhydrous sodium acetate, and 1.6 L of acetic anhydride. The stirred solution is refluxed for 3 hr and the acetic anhydride is then removed by distillation at 15-20 mm. The residue is extracted with three 875-mL portions of boiling toluene (Note 5), and the hot toluene extractions are filtered, combined, and concentrated to a total volume of 675 mL. Diethyl ether (675 mL) is added with stirring to the toluene solution and the mixture is chilled in an ice-water bath. The precipitate is removed by filtration and washed with 250 mL of diethyl ether to give 328-403 g (68-83%) of colorless to very light tan crystals, mp 65-67°C [lit.[2] mp 69-

70°C] (Note 6). A second crop of 63-24 g (13-5%), mp 65-68°C, is obtained by concentrating the filtrate to 275 mL and chilling it in an ice-water bath.

C. 3-Acetyl 4- and 5-chloro-2-oxazolidinone. A 3-L, four-necked flask is equipped with a reflux condenser topped with a gas discharge tube, thermometer, fritted glass inlet tube extending to the bottom of the flask, and a glass sleeve for accepting an UV lamp (Note 7). The reaction vessel is charged with 258 g (2.0 mol) of 3-acetyl-2-oxazolidinone, 2 L of carbon tetrachloride, and several boiling chips. The mixture is heated to gentle reflux, the light source is turned on, and 155 g (2.18 mol) of chlorine gas (Note 8) is introduced at such a rate that no chlorine escapes from the condenser (Note 9). After the addition is complete, heating is discontinued and nitrogen is bubbled through the reaction mixture to remove the dissolved hydrogen chloride. The solvent is then removed on a rotary evaporator to give a yellow oil, which consists of a mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinones[3] and is used in Step D without further purification.

D. 3-Acetyl-2(3H)-oxazolone. The crude mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinone from Step C is placed in a 2-L, three-necked flask equipped with a thermometer, sealed mechanical stirrer, and gas discharge tube. The material is heated to 120°C with stirring, and the temperature is then slowly increased to 150°C and held there until the evolution of gas ceases (Note 10). The cooled, black reaction mixture is distilled at 20 mm. The fractions boiling up to 150°C are collected and redistilled through a 50-cm x 3-cm Vigreux column fitted with a variable take-off head. There is obtained 140-172 g (55-68%) of product, bp 108-112°C (24 mm), which solidifies, mp 35-37°C (Note 11).

E. 4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one. A solution of 63.5 g (0.5 mol) of 3-acetyl-2(3H)-oxazolone, 27.5 g (0.33 mol) of 2,3-dimethylbutadiene (Note 12) and 2.0 g of hydroquinone in 125 mL of benzene is heated at 160°C under nitrogen in a 360-mL Hastelloy C shaker tube (Note 13). After 12 hr, the pressure vessel is cooled to room temperature, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated another 12 hr at 160°C. The vessel is again cooled, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated at 160°C for a final 12 hr. The resulting mixture is distilled to give 36.4-40.3 g (35-39%) of crude product, bp 115-130°C (0.5 mm), which solidifies (Notes 14 and 15). This material can be recrystallized by adding 36.4 g of melted product to 50 mL of boiling hexane, followed by cooling to give 27.6 g (26%) of crystals, mp 72-78°C (Note 16).

F. 6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol. A solution of 26.1 g (0.125 mol) of 4-acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one and 42.0 g (0.75 mol) of potassium hydroxide in 200 mL of methanol and 100 mL of water is refluxed for 36 hr. The resulting mixture is exhaustively extracted with diethyl ether using a liquid-liquid continuous extraction apparatus. The ethereal extract is concentrated on a rotary evaporator and the residue is taken up in 150 mL of methylene chloride. The resulting solution is dried over anhydrous sodium sulfate, the drying agent is removed by filtration, and the filtrate is concentrated to dryness. The solid residue (16.5 g) is recrystallized from 100 mL of diethyl ether to give 11.2 g (64%) of colorless crystals, mp 63-65.5°C. A second crop of 2.3 g (13%) is obtained by concentrating the mother liquor to 50 mL and chilling in an ice-water bath (Note 17).

2. Notes

1. The checkers obtained 2-aminoethanol, diethyl carbonate, and anhydrous sodium methoxide from the Aldrich Chemical Company.

2. About 625 mL (theoretical: 583 mL) of ethanol is collected. If the reaction is stopped before this volume is collected, the yield is reduced.

3. If the reaction mixture cools below 60°C, the product solidifies in the flask.

4. The product shows the following ^{1}H NMR spectrum (d_6-DMSO) δ: 3.3-3.8 (m, 2 H), 4.2-4.6 (m, 2 H), 6.5-7.5 (br s, 1 H) and is analytically pure. Anal. Calcd for $C_3H_5NO_2$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.61; H, 5.70; N, 16.06. The submitters report that they obtained pure material, mp 89-90°C, after three recrystallizations from chloroform.

5. This is conveniently done by adding the toluene to the residue in the flask, heating to reflux in an oil bath and then filtering the hot mixture.

6. This material shows the following ^{1}H NMR spectrum ($CDCl_3$) δ: 2.49 (s, 3 H), 3.8-4.7 (complex m, 4 H) and has acceptable analysis. Anal. Calcd for $C_5H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.49; H, 5.40; N, 10.99. The submitters report that they obtained colorless, analytically pure material, mp 69-70°C, after three recrystallizations from benzene.

7. The submitters used a Philips HPK 125-watt high-pressure mercury vapor lamp. The sleeve is 2-mm Pyrex glass with an NS45 ground joint. The lamp does not require cooling. The checkers obtained equally good results by shining a Westinghouse 250-watt sun lamp on the reaction flask from a distance of 25 cm.

8. The chlorine gas is passed successively through three wash bottles. The center bottle is filled with concentrated sulfuric acid and the other two are left empty to serve as safety traps.

9. The photochlorination takes 4-6 hr. The hydrogen chloride evolved is absorbed in water.

10. Dehydrochlorination begins at about 120°C. The temperature is raised about 10°C/hr to 150°C to avoid vigorous gas evolution. The elimination of hydrogen chloride is complete after 5-6 hr.

11. The submitters report yields of 150-200 g, and that analytically pure material boils at 110°C (24 mm) and melts at 35-37°C after recrystallization from diethyl ether. The material obtained by the checkers showed a satisfactory analysis without further purification. Anal. Calcd for $C_5H_5NO_3$: C, 47.25; H, 3.97; N, 11.02. Found: C, 46.81; H, 4.00; N, 11.21. The material shows the following ^1H NMR spectrum ($CDCl_3$) δ: 2.63 (s, 3 H), 6.90 (d, 1 H, J = 2.5), 7.30 (d, 1 H, J = 2.5); IR (CCl_4) cm^{-1}: 1880, 1735 (C=0).

12. The sample of 2,3-dimethylbutadiene was obtained from the Aldrich Chemical Company.

13. The submitters employed a nickel autoclave and noted that product from Step D may contain a small amount of hydrogen chloride or chlorinated material than can adversely affect a stainless steel pressure vessel. Hastelloy C is a high-nickel alloy.

14. The submitters obtained 48.0 g of product and 33.5 g of recovered starting material, bp 110°C (24 mm). The checkers found that the forerun collected at 108-112°C (24 mm) contained starting material, but it was highly contaminated with unidentified by-products.

15. The checkers obtained erratic results in this step, possibly because of surface effects or trace impurities in the pressure vessel. In two other runs, only 16.8-18.8 g of crude product were obtained. In one case, high boiling oligomers were formed, but none of the desired product was produced. Impurities in the diene or dienophile did not appear to be the problem since runs which employed recrystallized 3-acetyl-2(3H)-oxazolone and redistilled 2,3-dimethylbutadiene also gave variable results.

16. The submitters report pure product with bp 135-137°C (1.2 mm) and mp 78-80°C after recrystallization from chloroform. The checkers found that recrystallization from chloroform gave very poor recovery of product with mp 75-78°C. Material with mp 72-78°C is pure by NMR, mass spectroscopy, and combustion analysis; ^1H NMR ($CDCl_3$) δ: 1.70 (s, 6 H), 2.33 (m, 4 H), 2.45 (s, 3 H), 4.40 (d of t, 1 H, J = 9.0, 4.5), 4.83 (d of t, 1 H, J = 9.0, 4.5); IR (KBr) cm^{-1}: 1780, 1690. Mass spectrum m/e calculated: 209.1051. Found: 209.1030. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.10; N, 6.67.

17. The product shows the following ^1H NMR spectrum ($CDCl_3$) δ: 1.60 (s, 6 H), 2.13 (br m, 4 H), 2.30 (s, 3 H), 3.00 (m, 1 H), 3.80 (m, 1 H) and is analytically pure. Anal. Calcd for $C_8H_{15}ON$: C, 66.35; H, 10.71; N, 9.92. Found: C, 66.17, H, 10.48; N, 10.26.

3. Discussion

The dienophile, 3-acetyl-2(3H)-oxazolone[4], is an attractive intermediate for the synthesis of vicinal aminoalcohols with cis configurations. It reacts with 1,3-dienes, even under quite mild conditions, to form (4+2) cycloadducts.[5,6] Its high reactivity with deactivated 1,3-dienes is noteworthy. This property is present also in 2(3H)-oxazolone[4] which can be obtained easily through solvolysis of 3-acetyl-2(3H)-oxazolone in methanol. 3-Acetyl-2(3H)-oxazolone, on UV irradiation in the presence of a sensitizer, combines easily with olefins to form (2+2) cycloadducts,[7] the hydrolysis of which leads to the class of cis-2-aminocyclobutanols.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Aminoethanol: Ethanol, 2-amino- (8,9); (141-43-5)

Diethyl carbonate: Carbonic acid, diethyl ester (8,9); (105-58-8)

2-Oxazolidinone (8,9); (497-25-6)

3-Acetyl-2-oxazolidinone: 2-Oxazolidinone, 3-acetyl- (8,9); (1432-43-5)

3-Acetyl-5-chloro-2-oxazolidinone: 2-Oxazolidinone, 3-acetyl-5-chloro- (9); (60759-48-0)

3-Acetyl-2(3H)-oxazolone: 2(3H)-Oxazolone, 3-acetyl- (9); (60759-49-1)

2,3-Dimethylbutadiene: 1,3-Butadiene, 2,3-dimethyl- (8,9); (513-81-5)

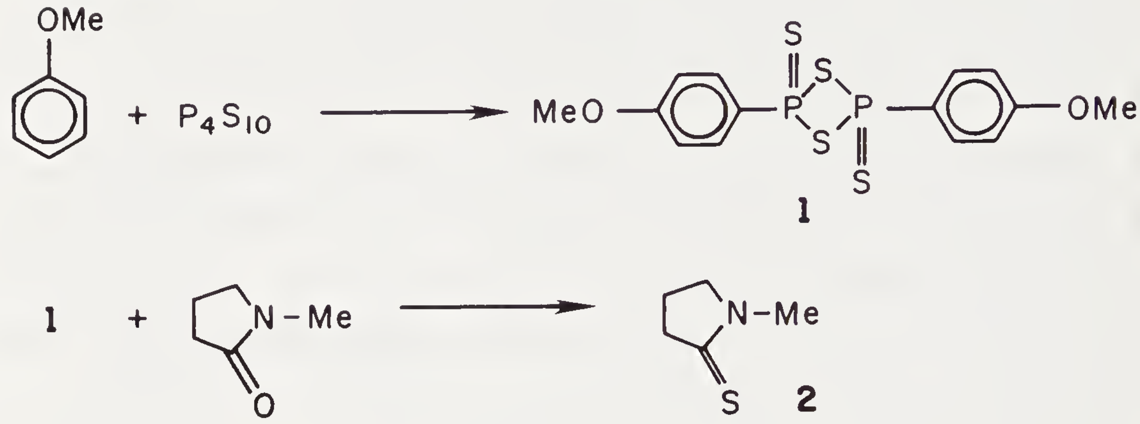
Hydroquinone (8); 1,4-Benzenediol (9); (123-31-9)

4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one: 2(3H)-Benzoxazolone, 3-acetyl-3a,4,7,7a-tetrahydro-5,6-dimethyl- (9); (65948-43-8)

6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol: 3-Cyclohexen-1-ol, 6-amino-3,4-dimethyl-, cis- (9); (65948-45-0)

THIATION WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE 2,4-DISULFIDE: N-METHYLTHIOPYRROLIDONE

(2-Pyrrolidinethione, 1-methyl-)



Submitted by I. Thomsen, K. Clausen, S. Scheibye, and S.-O. Lawesson[1].

Checked by Clayton H. Heathcock, Mark Sanner and Terry Rosen.

1. Procedure

Caution! Preparation of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide must be carried out in an efficient hood because hydrogen sulfide is evolved.

A. *2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide* (**1**). A dry 1-L, three-necked, round-bottomed flask, fitted with a reflux condenser, mechanical stirrer, and ground-glass stopper, is charged with 111.0 g (0.25 mol) of phosphorus sulfide, P_4S_{10} (Note 1) and 270 g (2.5 mol) of anisole (Note 1). Stirring is commenced and the mixture is heated at reflux temperature by use of a heating mantle. After 1 hr, the solution is homogeneous and after a second hour 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**1**) begins to precipitate. The reaction mixture is allowed to cool to room temperature and the precipitate is filtered (Note 2) and washed with anhydrous ether (2 x 50 mL) and 50 mL of anhydrous chloroform (free of alcohols) to yield 160-165 g (79-82%) of pale yellow crystals, mp 228°C (Notes 3 and 4).

B. N-Methylthiopyrrolidone (**2**). A 200-mL, three-necked, round-bottomed flask is fitted with a rubber septum, thermometer, magnetic stirring bar, and reflux condenser equipped with a nitrogen bubbler. The flask is charged with 19.8 g (19.3 mL, 0.20 mol) of N-methylpyrrolidone (Note 5) and 40.4 g (0.10 mol) of 1, whereupon the temperature of the reaction mixture increases to 75-80°C. After 5 min, 35 mL of benzene (Note 6) is added by syringe and the mixture is stirred while being brought to reflux (Note 7). The mixture is heated at reflux for 2 hr (Note 8) and then cooled to room temperature, whereupon it again becomes heterogeneous. The benzene is removed with the aid of a rotary evaporator and the resulting yellow slurry is distilled under reduced pressure through a 5-cm Vigreux column to provide 23.0 g (100%) of N-methylthiopyrrolidone (**2**) as a yellow liquid, bp 94-97°C/0.03 mm (Note 9).

2. Notes

1. Commercial phosphorus sulfide, P_4S_{10}, is used without purification. Checkers used P_4S_{10} from Matheson, Coleman and Bell and from Alfa Products, Morton/Thiokol, Inc. Best results (yield, melting point) were obtained with the Alfa sample, mp 291-295°C.

2. Excess anisole (137 g) can be recovered by distillation of the filtrate.

3. The product is somewhat hygroscopic and should be stored in an air-tight container. It is also available as Lawesson's reagent from Aldrich, Fluka, and from Merck-Schuchard.

4. The checkers obtained 176 g (87%) of 1, mp 228-231°C.

5. Commercial material from the Aldrich Chemical Company was stored over 4Å molecular sieves.

6. Benzene was distilled from and stored over sodium wire.

7. During this operation most of the yellow solid gradually dissolves, affording a clear yellow solution with small amounts of suspended solid. When reflux begins, the internal temperature of the reaction mixture is 95°C.

8. The reaction time can be decreased to 3 min by the use of toluene as solvent.

9. The purified product freezes when stored in a refrigerator. The spectral properties are as follows: ^1H NMR ($CDCl_3$) δ: 2.07 (quintet, 2 H, J = 7), 3.03 (t, 2 H, J = 7), 3.29 (s, 3 H), 3.77 (t, 2 H, J = 7). IR (neat): 1520 cm^{-1}.

3. Discussion

A variety of thiating reagents are known: H_2S,[2] H_2S/HCl,[3] H_2S_2/HCl,[4] $(Et_2Al)_2S$,[5] $(EtAlS)_n$,[6] SiS_2,[7] B_2S_3,[7] $PCl_5/Al_2S_3/Na_2SO_4$,[8] Na_2S/H_2SO_4,[9] P_2S_5[10] P_2S_5/pyridine,[11] P_2S_5/NEt_3,[12] $P_2S_5/NaHCO_3$,[13] $RPS(OR^1)_2$,[14] $PSCl_x(NMe_2)_{3-x}$ (X = 0-3),[15] and SCNCOOEt.[16] The reagent described here, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (1)[17] offers a number of advantages as a thiating reagent. It is easily prepared in a simple one-step procedure employing commercially available starting materials. It has a satisfactory shelf life, provided that it is protected from moisture. In contrast to commercial P_4S_{10}, compound **1** is a well-defined reagent which gives reproducible results, usually in high yield. Under defined conditions, certain selectivity has been observed.[18-20] Other methods for the preparation of analogs of **1** have been described.[21-23]

The thiation procedure described here[24] is an example of a general synthetic method for the conversion of carbonyl to thiocarbonyl groups. Similar transformations have been carried out with ketones,[25] carboxamides,[26-30] esters,[31-32] thioesters,[31] lactones,[18,33] thiolactones,[18] imides,[24] enaminones,[34] and protected peptides.[35]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide: Phosphonotrithioic acid, (p-methoxyphenyl)-bimol cyclic anhydrosulfide (8); 1,3,2,4-Dithiaphosphetane, 2,4-bis(4-methoxyphenyl)- 2,4-disulfide (9); 19172-47-5

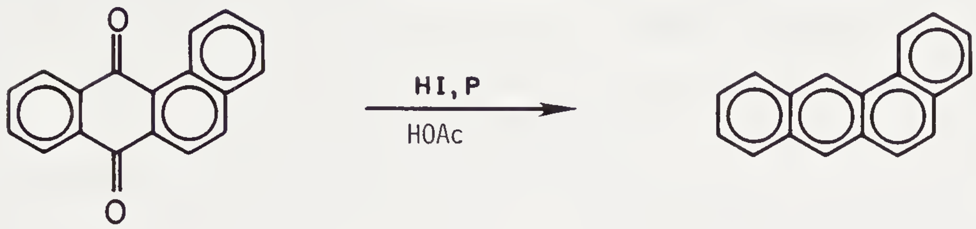
N-Methylthiopyrrolidone: 1-Methyl-2 (3H)-pyrrolethione, dihydro- (8); 2-Pyrrolidinethione, 1-methyl- (9); 10441-57-3

N-Methylpyrrolidone: 2-Pyrrolidinone, 1-methyl- (8,9); 872-50-4

Anisole (8); Benzene, methoxy- (9)- ; 100-66-3

Phosphorus sulfide (8,9); 12066-62-5

REDUCTION OF QUINONES WITH HYDRIODIC ACID: BENZ[a]ANTHRACENE



Submitted by Maria Konieczny and Ronald G. Harvey[1].

Checked by Gregory A. Reed and Carl R. Johnson.

1. Procedure

Caution! Benz[a]anthracene and benzene are known carcinogens. All appropriate precautions should be taken in handling these substances.

A 500-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and an efficient condenser, and charged with 10.3 g (0.04 mol) of benz[a]anthracene-7,12-dione (Note 1), 5 g (0.16 mol) of red phosphorus (Note 2) and 100 mL of glacial acetic acid. The stirred suspension is heated to reflux, and 60 mL of 56% hydriodic acid (approx. 0.44 mol) (Note 3) is introduced through the condenser. The suspension is heated at reflux for 24 hr. The hot reaction mixture is poured into 500 mL of distilled water containing ~ 30 g of sodium bisulfite. The suspension is stirred for 16 hr and filtered. The dry filter cake is transferred to a beaker and treated with sufficient hot dichloromethane (~ 120 mL) to dissolve all of the benz[a]anthracene, and the mixture is filtered once again to remove the residual phosphorus. The volume of the filtrate is reduced to 40 mL. The solution is adsorbed on basic alumina, activity I (Note 4). A chromatography column (2-cm x 40-cm) is slurry-packed with ca. 10 g of basic alumina and the benz[a]anthracene adsorbed on alumina is added to the top of the column. Elution with 5% benzene in hexane (occasional rinsing of the column tip with benzene to remove crystallized product may be necessary) and evaporation of the solvent in a rotary evaporator affords 7.7-7.9 g (84-87%) of pure, white benz[a]anthracene, mp 159.5-160°C (Note 5).

2. Notes

1. Benz[a]anthracene-7,12-dione, available from Eastman Organic Chemicals, was used without further purification.

2. Phosphorus, which serves to scavenge the I_2 produced, can be omitted. However, the product tends to retain traces of a yellow impurity which is difficult to remove.

3. The hydriodic acid employed was a 56% aqueous solution preserved with ~ 0.8% hypophosphorous acid obtained from Fisher Scientific Co. Once a bottle is opened, the contents tend to deteriorate, becoming dark-colored in less than 2 days. However, shelf life can be extended indefinitely if the container is purged with dry nitrogen before resealing.

4. Alumina sufficient to adsorb the complete solution is added, then the solvent is removed under vacuum. While benz[a]anthracene, mp 157-158°C, sufficiently pure for most purposes, can be obtained by crystallization of the crude product from ethanol-water, "filtration" through alumina removes residual, colored impurities, affording a pure, white product.

5. Pure benz[a]anthracene has been reported to melt at 158-159°,[2] 160°,[3] and 167°C.[4] The submitters report a mp of 164-164.5°C. The submitters conducted this preparation on a scale five times larger and reported yields up to 95%.

3. Discussion

The synthetic procedure described is based on that reported earlier for the synthesis on a smaller scale of anthracene, benz[a]anthracene, chrysene, dibenz[a,c]anthracene, and phenanthrene[5] in excellent yields from the corresponding quinones.[6] Although reduction of quinones with HI and phosphorus was described in the older literature, relatively drastic conditions were employed and mixtures of polyhydrogenated derivatives were the principal products.[7] The relatively milder experimental procedure employed herein appears generally applicable to the reduction of both ortho- and para-quinones directly to the fully aromatic polycyclic arenes. The method is apparently inapplicable to quinones having an olefinic bond, such as o-naphthoquinone, since an analogous reaction of the latter provides a product of undetermined structure (unpublished result). As shown previously,[6] phenols and hydroquinones, implicated as intermediates in the reduction of quinones by HI, can also be smoothly deoxygenated to fully aromatic polycyclic arenes under conditions similar to those described herein.

Although previous experience indicates that phosphorus is not essential for these reductions,[6,8] purification of the product is more difficult with its omission. With hydrocarbons sensitive to further reduction, phosphorus can have a deleterious effect through promotion of hydrogenation of the desired product. Whether or not phosphorus should be employed in an individual case will be dictated by experience with the particular compound and by the degree of purity required.

While the reduction of polycyclic quinones to phenols, hydroquinones, dihydrodiols, dihydro arenes and arenes by a variety of reagents has been described, no entirely satisfactory general method is currently available for reduction directly to the fully aromatic arenes. Reagents previously employed for this purpose include $LiAlH_4$,[9,10] $NaBH_4$,[11] $NaBH_4$-BF_3,[11a,12] diborane,[12] aluminum and cyclohexanol,[13] zinc dust distillation,[14] and diphenylsilane.[15] These methods commonly furnish lower yields and are less general than the present procedure.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

Benz[a]anthracene (8,9); (56-55-3)

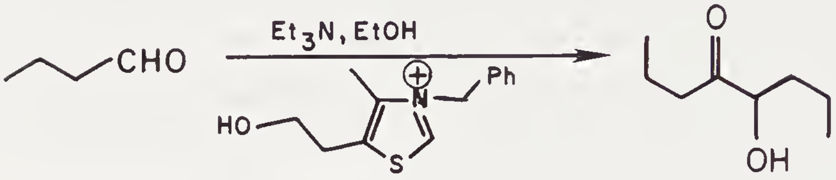
Benz[a]anthracene-7,12-dione (8,9); (2498-66-0)

Phosphorus (8,9); (7723-14-0)

Hydriodic acid (8,9); (10034-85-2)

ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS: BUTYROIN

(4-Octanone, 5-hydroxy-)



Submitted by H. Stetter and H. Kuhlmann[1].

Checked by Sharbil J. Firsan and Robert M. Coates.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube. The flask is charged with 13.4 g (0.05 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (Note 1), 72.1 g (1.0 mol) of butyraldehyde (Note 2), 30.3 g (0.3 mol) of triethylamine (Note 2), and 300 mL of absolute ethanol. A slow stream of nitrogen (Note 3) is begun, and the mixture is stirred and heated in an oil bath at 80°C. After 1.5 hr the reaction mixture is cooled to room temperature and concentrated by rotary evaporation. The residual yellow liquid is poured into 500 mL of water contained in a separatory funnel, and the flask is rinsed with 150 mL of dichloromethane which is then used to extract the aqueous mixture. The aqueous layer is extracted with a second 150-mL portion of dichloromethane. The combined organic phases are washed with 300 mL of saturated sodium bicarbonate and with 300 mL of water. The dichloromethane is removed by rotary evaporation under slightly diminished pressure. Distillation through a 20-cm Vigreux column gives 51-54 g (71-74%) of product as a colorless to light yellow liquid, n_D^{20} 1.4309, bp 90-92°C (13-14 mm) (Notes 4 and 5).

2. Notes

1. The catalyst, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, is supplied by Fluka AG, Buchs, Switzerland, and by Tridom Chemical, Inc., Hauppauge, New York. The thiazolium salt may also be prepared as described below[2] by benzylation of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole which is commercially available from E. Merck, Darmstadt, West Germany, and Columbia Organic Chemicals Co., Inc., Columbia, SC. The acetonitrile used by the checkers was dried over Linde 3Å molecular sieves[3] and distilled under nitrogen, bp 77-78°C. The same yield of thiazolium salt was obtained by the checkers when benzyl chloride and acetonitrile from commercial sources were used without purification.

A 250-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube, and a stopper. The flask is charged with 14.3 g (0.1 mol) of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, 12.7 g (0.1 mol) of freshly distilled benzyl chloride, and 50 mL of dry acetonitrile. The mixture is heated at reflux for 24 hr and cooled to room temperature. Crystallization is induced by scratching or seeding. The solid is collected by suction filtration, washed colorless with two 50-mL portions of acetonitrile, and dried partially in the air. Drying is completed under reduced pressure by gentle rotation on a rotary evaporator heated with a water bath at about 90°C. The yield of thiazolium salt, mp 141-143°C, is 18.2-19.6 g (67-73%).

2. Butyraldehyde is supplied by Aldrich Chemical Co., Inc., and Eastman Organic Chemicals. The aldehyde was freshly distilled before use. Triethylamine was dried over potassium hydroxide pellets and distilled.

3. The submitters recommend that the nitrogen stream be passed through a bubbler and that the flow rate be adjusted to ca. one bubble per second. If the nitrogen flow is too fast, some of the butyraldehyde will be swept out of the flask.

4. The procedure may be conducted on a larger scale in which case the proportion of catalyst and base are reduced. The submitters report that they obtained 169 g (78%) of butyroin from 216.3 g (3.0 mol) of butyraldehyde, 26.8 (0.1 mol) of thiazolium catalyst, 60.6 g (0.6 mol) of triethylamine, and 600 mL of absolute ethanol. Although the scale may be increased further, appropriate precautions should be taken to control the reaction. For example, the aldehyde may be added in portions or the flask may be cooled initially.

5. The product obtained by the checkers boiled at 86-87.5°C (15-16 mm). A boiling point of 85-87°C (12-13 mm) and an index of refraction n_D^{20} 1.4325 have been recorded for butyroin.[4] The product exhibits the following spectral characteristics: IR (neat) cm^{-1}: 3505 and 1704; ^1H NMR (CCl_4) δ: 3.98 (m, 1 H, CHOH), 3.31 (s, 1 H, OH), 2.41 (t, 2 H, J = 7, $CH_2C{=}O$), 1.64 (sextet, 2 H, J = 7, $CH_2CH_2C{=}O$), 1.56-1.18 (m, 4 H, 2 CH_2), 0.94 (unsymmetrical t, 6 H, 2 CH_3).

3. Discussion

This procedure is representative of a new general method for the preparation of noncyclic acyloins by thiazolium-catalyzed dimerization of aldehydes in the presence of weak bases (Table I).[5] The advantages of this method over the classical reductive coupling of esters[6] or the modern variation in which the intermediate enediolate is trapped by silylation,[4,7] are the simplicity of the procedure, the inexpensive materials used, and the purity of the products obtained. For volatile aldehydes such as acetaldehyde and propionaldehyde the reaction is conducted without solvent in a small, heated autoclave. With the exception of furoin the preparation of benzoins from aromatic aldehydes is best carried out with a different thiazolium catalyst bearing an N-methyl or N-ethyl substituent, instead of the N-benzyl group.[5] Benzoins have usually been prepared by cyanide-catalyzed condensation of aromatic and heterocyclic aldehydes.[8,9,10] Unsymmetrical acyloins may be obtained by thiazolium-catalyzed cross-condensation of two different aldehydes.[11] The thiazolium ion-catalyzed cyclization of 1,5-dialdehydes to cyclic acyloins has been reported.[12]

Although the catalysis of the dimerization of aldehydes to acyloins by thiazolium ion has been known for some time,[13] the development of procedures using anhydrous solvents which give satisfactory yields of acyloins on a preparative scale was first realized in the submitters' laboratories.[5] The mechanism proposed by Breslow[13a] for the thiazolium ion-catalyzed reactions is similar to the Lapworth mechanism[14] for the benzoin condensation with a thiazolium ylide replacing the cyanide ion. Similar mechanisms are involved in many important enzyme-catalyzed transformations which require thiamine as a co-factor. The combination of thiazolium salts and weak bases has also been utilized to catalyze the conjugate addition of aldehydes to electron-deficient double bonds.[2]

Butyroin has been prepared by reductive condensation of ethyl butyrate with sodium in xylene,[6b] or with sodium in the presence of chlorotrimethylsilane.[7] and by reduction of 4,5-octanedione with sodium 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-sulfinate in the presence of magnesium chloride[15] or with thiophenol in the presence of iron polyphthalocyanine as electron transfer agent.[16] This acyloin has also been obtained by oxidation of (E)-4-octene with potassium permanganate[17] and by reaction of propylmagnesium bromide with nickel tetracarbonyl.[18]

Acyloins are useful starting materials for the preparation of a wide variety of heterocycles (e.g., oxazoles[19] and imidazoles[20]) and carbocyclic compounds (e.g., phenols[21]). Acyloins lead to 1,2-diols by reduction, and to 1,2-diketones by mild oxidation.

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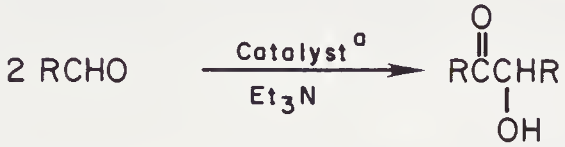
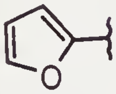
TABLE I

ACYLOINS PREPARED BY THIAZOLIUM ION-CATALYZED CONDENSATION OF ALDEHYDES[5]



R	Yield(%)	Bp or mp (°C)
C_4H_9	79	83 (2.2 mm)
C_5H_{11}	81	90 (1.5 mm)
C_7H_{15}	83[b]	39
C_9H_{19}	85[b]	53
$C_{11}H_{23}$	83[b]	62
	80[c,d]	136

[a] 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride. [b] The product was isolated by pouring the ethanolic solution into well-stirred, ice-cold water, filtering, and recrystallizing from aqueous ethanol. The solutions should be ice-cold for the isolation of the low-melting acyloins. The products may also be isolated by extraction as described for butyroin. [c] In this case furoin crystallized from the ethanolic solution upon cooling. [d] The following somewhat simpler procedure may also be used. A solution of 13.4 g (0.05 mol) of catalyst, 96.1 g (1.0 mol) of 2-furaldehyde, 300 mL of absolute ethanol, and 30.3 g (0.3 mol) of triethylamine is stirred at room temperature for 12 hr. The product (84.5 g, 88%) crystallizes directly from solution and is isolated by filtration.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Benzyl chloride: Toluene, α-chloro- (8); Benzene, (chloromethyl)- (9); (100-44-7).

Butyraldehyde (8); Butanal (9); (123-72-8)

Butyroin: 4-Octanone, 5-hydroxy- (8,9); (496-77-5)

2-Furaldehyde (8); 2-Furancarboxaldehyde (9); (98-01-1)

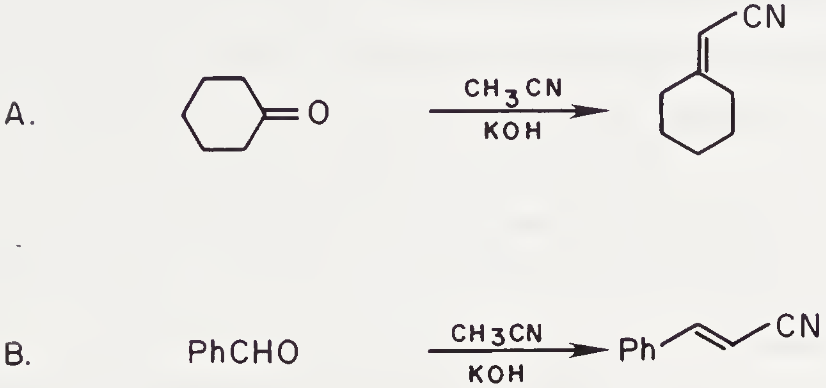
5-(2-Hydroxyethyl)-4-methyl-1,3-thiazole: 5-Thiazoleethanol, 4-methyl- (8,9); (137-00-8)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride: Thiazolium, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-, chloride (8); Thiazolium, 5-(2-hydroxyethyl)-4-methyl-3-(phenylmethyl)-, chloride (9); (4568-71-2)

SYNTHESIS OF α,β-UNSATURATED NITRILES FROM ACETONITRILE: PREPARATION OF CYCLOHEXYLIDENEACETONITRILE AND CINNAMONITRILE

(Acetonitrile, cyclohexylidene- and 2-Propenenitrile, 3-phenyl, (E)-)



Submitted by Stephen A. DiBiase, James R. Beadle, and George W. Gokel[1].

Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. Cyclohexylideneacetonitrile. A 1-L three-necked, round-bottomed flask equipped with a reflux condenser, mechanical stirrer and addition funnel, is charged with potassium hydroxide (85% pellets, 33.0 g, 0.5 mol, Note 1) and acetonitrile (250 mL, Notes 2 and 3). The mixture is brought to reflux and a solution of cyclohexanone (49 g, 0.5 mol, Note 4) in acetonitrile (100 mL) is added over a period of 0.5-1.0 hr. Heating at reflux is continued for 2 hr (Note 5) after the addition is complete and the hot solution is then poured onto cracked ice (600 g). The resulting binary mixture is separated and the aqueous phase is extracted with ether (3 x 200 mL). The combined organic extracts are evaporated under reduced pressure, or may be placed in a 2-L Erlenmeyer flask containing several boiling chips and the volume reduced on a steam bath (internal temperature ca. 50°C). The resulting sweet-smelling, yellow to yellow-orange oil is transferred to a 1- or 2-L, three-necked, round-bottomed flask (depending on whether internal or external steam generation is used) and steam distilled (bp 81-99°C, Note 6). The distillate is extracted with three to five 200-mL portions of ether until the aqueous phase is clear (Note 7). The ether phase is washed with brine (2 x 100 mL), dried over sodium sulfate and evaporated under reduced pressure to give a pale yellow oil (29-36 g, 48-60%) which consists of a mixture of isomers (α,β 80-83%, β,γ 17-20%, Note 8).

Isolation of the pure α,β *isomer*. A 250-mL Erlenmeyer flask equipped with a magnetic stirring bar is charged with the isomeric nitriles (20 g, 0.165 mol), prepared in Part A above, and carbon tetrachloride (20 mL). A solution of bromine in carbon tetrachloride (1/9, v/v, ca. 25-30 mL) is added dropwise until the color of excess bromine persists. The reaction vessel is cooled in an ice bath for 30 min, filtered by gravity and the solvent evaporated under reduced pressure. The crude oil is distilled at reduced pressure (bp 40-42°C/0.15 mm) to give a colorless liquid (11-15 g, 55-75%) which is the pure α,β-isomer (Notes 9 and 10).

B. Preparation of E- and Z-Cinnamonitrile. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel is charged with potassium hydroxide pellets (33 g, 0.5 mol, Note 1) and acetonitrile (400 mL, Note 2). The mixture is brought to reflux under nitrogen and a solution of benzaldehyde (53 g, 0.5 mol, Note 4) in acetonitrile (100 mL) is added in a stream (1-2 min). After addition, stirring is continued for 10 min (Note 5) and the hot solution is then poured onto 500 g of cracked ice in a 1-L beaker. After being cooled for a few minutes, the two-phase mixture is transferred to a 2-L, three-necked flask and steam distilled (Note 11). The distillate is transferred to a separatory funnel, the upper aqueous phase is separated and then extracted with two 500-mL portions of ether (Note 7). The combined organic material is dried briefly over Na_2SO_4 and the ether evaporated to yield pure cinnamonitrile (20-29 g, 31-45%) as a pale yellow oil (E/Z ratio ca. 5.5, Note 12).

2. Notes

1. Potassium hydroxide (85% pellets, AR grade) should be as fresh as possible (see Note 5).

2. Acetonitrile (99%) was obtained from Aldrich Chemical Company, Inc. and may be used without purification.

3. The yield of product is dependent on concentration. An increase in the amount of acetonitrile in Part A to ca. 1000 mL increases the yield of the isomer mixture to 65-75% without affecting isomer distribution. Further dilution to ca. 5000 mL increases the yield to 80-85%.

4. Cyclohexanone and benzaldehyde were purchased from either Aldrich Chemical Company, Inc., or Eastman Organic Chemicals and used without additional purification.

5. The reaction time depends on the quality of the potassium hydroxide employed. An induction period is often observed when older potassium hydroxide samples are used, possibly because surface formation of carbonates reduces the solubility of the salt in acetonitrile. An attempt was made to monitor the cinnamonitrile reaction by GLC, following loss of starting

material. Although formation of the product was observed and reached a maximum, the starting material peak never completely disappeared. Prolonged reaction times (greater than 2 hr) resulted in failure to isolate any of the desired product. Reaction times of less than 30 min gave the expected yields. Undissolved potassium hydroxide was observed in the reaction vessel when these reactions were terminated. At a column temperature of 150°C and a gas flow rate of ca. 60 mL/min (5-ft x 0.25-in column, 10% SE-30 on firebrick), the retention times are as follows: cyclohexylideneacetonitrile and isomer, 2.8 min; Z-cinnamonitrile, 3.0 min; E-cinnamonitrile, 3.7 min). The reaction may also be monitored by a 2,4-dinitrophenylhydrazone spot test.

6. Distillation may be conducted using an apparatus designed either for internal or external steam generation. The first 1000-mL portion of distillate contains ca. 35 g of product. An additional 500 mL of distillate yields less than 1 g. Vacuum distillation gave product in 22% yield.

7. To facilitate phase separation, solid sodium chloride was added to the aqueous layer.

8. The product thus obtained is of high purity. The trace of color may be removed by distillation at reduced pressure (bp 50°C/0.5 mm).

9. Bromination can be monitored by ^1H NMR in CCl_4. The vinyl protons are observed at 5.08 (α,β-isomer) and 5.65 ppm.

10. The ^1H NMR spectra (in CCl_4) for the two isomers are as follows: Cyclohexylideneacetonitrile: δ 1.25-2.0 (m, 6 H), 2.0-2.8 (m, 4 H, methylene protons), 5.08 (m, 1 H, olefin); 2-(1-cyclohexenyl)acetonitrile: 1.25-2.0 (m, 4 H), 2.0-2.8 [m, 4 H, $-(CH_2)_4-$], 3.05 (pseudo-s, 2 H, $-CH_2CN$), 5.65 (m, 1 H, olefin.

11. Steam distillation may be conducted using apparatus designed either for internal or external steam generation. Using internally-generated steam, 2.5 L of distillate was collected. The last 500 mL contained less than 1 g of product.

12. Isomer distribution and purity were assessed by GC (see Note 5). The ^1H NMR spectra (in CCl_4) for the pure isomers are as follows: E-isomer: δ 5.71 (d, 1 H, J = 17, ArCH=CH-CN; 7.44 (d, 1 H, J = 17, ArCH=CHCN), 7.3 (pseudo-s, 5 H, aromatic protons. Z-isomer: δ 5.31 (d, 1 H, J = 12, ArCH=CHCN), 6.98 (d, 1 H, J = 12, ArCH=CHCN), 7.3 (pseudo-s, 5 H, aromatic protons).

3. Discussion

Introduction of the two-carbon fragment is a cornerstone of synthetic methodology and many of the condensation reactions frequently used have been known for decades, if not for a century. Examples include the malonic ester[2] and acetoacetic ester[3] reactions, the Perkin[4] condensation, and the Doebner-Knoevenagel[5] reaction. Addition of the cyanomethyl group has been accomplished by a variety of methods,[6] mostly circuitous, and is certainly not in the group of classical reactions named above. The direct approach is found in a recent application of lithio trimethylsilylacetonitrile,[7] but the difference in expense and convenience between using this method and a mixture of potassium hydroxide and acetonitrile is manifest.

The direct synthesis of α,β-unsaturated nitriles can be accomplished by treating the appropriate carbonyl compound with potassium hydroxide in acetonitrile.[8] In order for direct condensation to succeed, acetonitrile must be deprotonated by the relatively weak base potassium hydroxide and the carbanion thus formed must add to the carbonyl. The cyanohydrin is presumably dehydrated to leave the α,β-unsaturated compound which may or may not isomerize in the medium. We have run this reaction with a large number of carbonyl compounds[8] and have found that it is most successful for aromatic aldehydes (36-86%) and other nonenolizable carbonyl compounds such as benzophenone (84%). Yields are also acceptable for most cyclic ketones with six or more carbons in the ring (e.g., 2-methylcyclohexanone, 78%; cis-octalone, 80%; cycloheptanone, 78%; cyclooctanone, 66%, cyclododecanone, 45%), and for aliphatic ketones having three or more carbons bonded on each side (e.g., diethyl ketone, 35%; di-n-propyl ketone, 65%, di-n-butyl ketone 65%). Ketones which are sterically hindered (camphor) or highly enolized (cyclopentanone) are not useful substrates in this reaction.

We present here examples of this condensation with an aromatic aldehyde and a cyclic ketone. Both of these examples are useful because, although other methods are available for their preparation, problems often attend these syntheses. In the synthesis of cyclohexylideneacetonitrile, for example, the standard method[9] results exclusively in the β,γ-isomer and none of the α,β-isomer. In Part A of this procedure, cyclohexanone is condensed with acetonitrile to give predominantly the conjugated isomer (80-83%) which is then separated from the nonconjugated isomer by selective bromination.

The procedures presented here are simple, inexpensive, and may be used on a large scale. The use of potassium hydroxide in this reaction may, however, prove incompatible with certain base-sensitive functional groups.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclohexylideneacetonitrile: $\Delta^{1,\alpha}$-Cyclohexaneacetonitrile (8); Acetonitrile, cyclohexylidene (9); (4435-18-1)

Cinnamonitrile (8); 2-Propenenitrile, 3-phenyl-, (E)- (9); (1885-38-7)

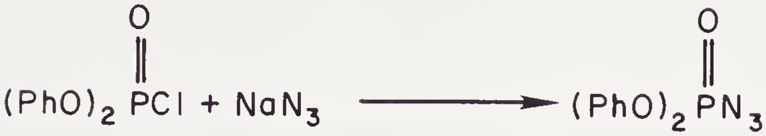
Cyclohexanone (8,9); (108-94-1)

Acetonitrile (8,9); (75-05-8)

Benzaldehyde (8,9); (100-52-7)

DIPHENYL PHOSPHORAZIDATE

(Phosphorazidic acid, diphenyl ester)



$$(PhO)_2\overset{O}{\overset{\|}{P}}Cl + NaN_3 \longrightarrow (PhO)_2\overset{O}{\overset{\|}{P}}N_3$$

Submitted by Takayuki Shioiri[1] and Shun-ichi Yamada[2].

Checked by Christina Bodurow and M. F. Semmelhack.

1. Procedure

A mixture of 56.8 g (0.21 mol) of diphenyl phosphorochloridate (Note 1), 16.3 g (0.25 mol) of sodium azide, and 300 mL of anhydrous acetone (Note 2) in a 500-mL round-bottomed flask fitted with a calcium chloride tube is stirred at 20-25°C for 21 hr. The lachrymatory mixture is filtered in a hood, and the filtrate is concentrated under reduced pressure. The residue is distilled through a short Vigreux column (Note 3). The yield of diphenyl phosphorazidate, bp 134-136°C (0.2 mm), is 49-52 g (84-89%) (Note 4).

2. Notes

1. Diphenyl phosphorochloridate (diphenyl chlorophosphate), from Aldrich Chemical Company, Inc., was used after purification by distillation at 165-168°C (5 mm).

2. Commercial acetone was dried over anhydrous potassium carbonate and distilled.

3. The bath temperature should be kept below 200°C to minimize decomposition of diphenyl phosphorazidate.[3]

4. Diphenyl phosphorazidate is a colorless non-explosive oil that can be kept for a long time without decomposition if it is protected against light[3] and moisture.

3. Discussion

The procedure described is essentially that of Shioiri and Yamada.[4] Diphenyl phosphorazidate is a useful and versatile reagent in organic synthesis.[5] It has been used for racemization-free peptide syntheses,[4,6,7] thiol ester synthesis,[8] a modified Curtius reaction,[6,9,10] an esterification of α-substituted carboxylic acid,[11] formation of diketopiperazines,[12] an alkyl azide synthesis,[13] phosphorylation of alcohols and amines,[14] and polymerization of amino acids and peptides.[15] Furthermore, diphenyl phosphorazidate acts as a nitrene source[3] and as a 1,3-dipole.[16,17] An example in the ring contraction of cyclic ketones to form cycloalkanecarboxylic acids is presented in the next procedure, this volume.

1. Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya 467, Japan.
2. Faculty of Pharmaceutical Sciences, Josai University, Saitama 350-02, Japan.
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5. For a review, see (a) Shioiri, T.; Yamada, S. *Yuki Gosei Kagaku Kyokai Shi (J. Synth. Org. Chem. Japan)* **1973**, *31*, 666; *Chem. Abstr.* **1974**, *81*, 13781a; (b) Shioiri, T. *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo (Ann. Rept. Pharm. Nagoya City University)* **1977**, *25*, 1.

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Appendix

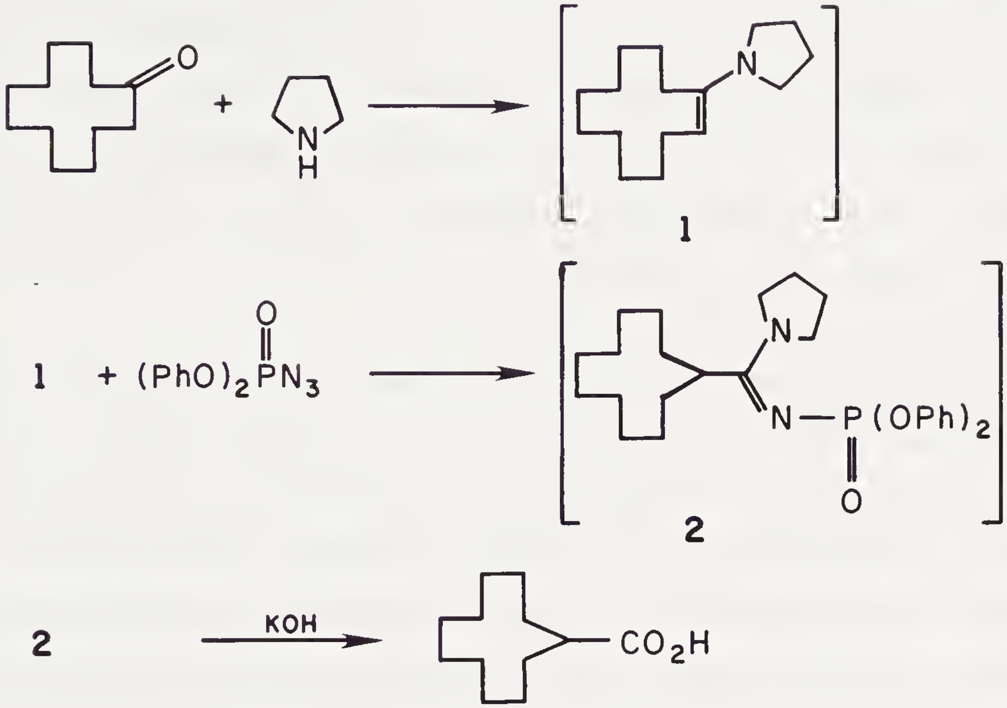
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diphenyl phosphorazidate: Phosphorazidic acid, diphenyl ester (8,9); (26386-88-9)

Diphenyl phosphorochloridate; Diphenyl chlorophosphate: Phosphorochloridic acid, diphenyl ester (8,9); (2524-64-3)

Sodium azide (8,9); (26628-22-8)

CYCLOUNDECANECARBOXYLIC ACID



Submitted by Yasumasa Hamada and Takayuki Shioiri[1].

Checked by M. F. Semmelhack and E. Spiess.

1. Procedure

To a 300-mL, round-bottomed flask fitted with a water separator, (Note 1) which contains 15 g of Linde 4Å molecular sieve 1/16-inch pellets and is filled with toluene, are added 7.3 g (0.04 mol) of cyclododecanone, 11.4 g (0.16 mol) of pyrrolidine, 100 mL of toluene, and 0.57 g (0.004 mol) of boron trifluoride etherate. The solution is heated under reflux for 20 hr. The water separator is replaced by a distillation head, and about 90 mL of the toluene is removed by distillation at atmospheric pressure. The residue containing 1-(N-pyrrolidino)-1-cyclododecene (**1**) is used in the next step without further purification (Note 2).

The crude enamine (**1**) is dissolved in 20 mL of toluene, and the solution is transferred (Note 3) to a 100-mL, three-necked flask equipped with a magnetic stirring bar, 50-mL dropping funnel, reflux condenser protected with a calcium chloride tube, and a thermometer immersed in the solution. A solution of 13.2 g (0.048 mol) of diphenyl phosphorazidate (Note 4; *WARNING*) in 20 mL of toluene is added with stirring during 30 min while the reaction temperature is maintained at about 25°C. The mixture is stirred for 4 hr at 25°C and heated at reflux for 1 hr. The mixture is transferred to a 300-mL, round-bottomed flask and most of the toluene is removed under reduced pressure to yield 23.7 g of a reddish-brown oil, **2** (Note 5).

Ethylene glycol (200 mL) and 40 g (0.71 mol) of potassium hydroxide are added to the residual oil. The mixture is heated at reflux for 24 hr, and then concentrated at 80-115°C (25 mm) (bath temperature is about 190°C) until 100 mL of the distillate is collected. The residue is dissolved in 300 mL of water, and cooled to room temperature. Carbon dioxide is introduced as a gas until the pH of the solution reaches 9. The mixture is washed with three 80-mL portions of diethyl ether (Note 6). The aqueous layer is acidified with about 53 mL of concentrated hydrochloric acid, and extracted with four 80-mL portions of benzene. The combined benzene extracts are washed with 50 mL of water and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give 4.5-5.5 g of a black-brown oil. Distillation of the oil at 110-115°C (0.1 mm) yields 3.5-3.8 g (40-48%) of cycloundecanecarboxylic acid as a colorless oil.

2. Notes

1. The apparatus described in *Organic Syntheses*[2] is satisfactory.

2. Pure 1-(N-pyrrolidino)-1-cyclododecene, bp 144°C (1.5 mm), may be isolated by distillation through a Vigreux column.

3. The original flask used for the enamine formation can be used after the attachment of a Y-shape tube fitted with a dropping funnel and a reflux condenser protected with a tube packed with a drying agent such as anhydrous calcium chloride.

4. Diphenyl phosphorazidate is prepared by the action of sodium azide with diphenyl phosphorochloridate (preceding procedure, this volume).[3] It is also available from Aldrich Chemical Co. and was used after purification by distillation at 134-136°C (0.2 mm). *WARNING*: Diphenyl phosphorazidate may produce explosive hydrogen azide when it is in contact with moisture for a long time. When diphenyl phosphorazidate, which has been stored for a long time, is used, it should be washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate before distillation.

5. Purification of 1 g of the crude oil was made by column chromatography using 50 g of Merck silica gel with 0.063-0.200-mm particles (catalog No. 7734) in a column 2.2- x 40-cm and 1:1 (V/V) ethyl acetate-hexane as eluant to give pure diphenyl (cycloundecyl-1-pyrrolidinylmethylene)phosphoramidate (2) as a colorless oil, 632 mg (78%). When a Merck precoated silica gel F254 thin layer plate, layer thickness 0.25 mm, is developed with 1:1 (V/V) ethyl acetate-hexane and visualized with ultraviolet light, the phosphoramidate appears at R_f 0.3. Thus the crude oil contained about 15 g of the phosphoramidate.

6. This procedure is designed primarily to remove phenol.

3. Discussion

Cycloundecanecarboxylic acid has been prepared by the bromination of cyclododecanone followed by the Favorskii rearrangement of 2-bromocyclododecanone.[4]

The present preparation illustrates a general and convenient method for ring contraction of cyclic ketones.[5] The first step is the usual procedure for the preparation of enamines. The second step involves 1,3-dipolar cycloaddition of diphenyl phosphorazidate to an enamine followed by ring contraction with evolution of nitrogen. Ethyl acetate and tetrahydrofuran can be used as a solvent in place of toluene. Pyrrolidine enamines from various cyclic ketones smoothly undergo the reaction under similar reaction conditions. Diphenyl (cycloalkyl-1-pyrrolidinylmethylene)phosphoramidates with 5,6,7, and 15 members in the ring have been prepared in yields of 68-76%.

The third step is hydrolysis of the N-phosphorylated amidines which is carried out by either acid or alkali depending on the substrate.

Similar reaction sequences can be used successfully to convert alkyl aryl ketones to α-arylalkanoic acids.[6]

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6. Shioiri, T.; Kawai, N. *J. Org. Chem.* **1978**, *43*, 2936.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diphenyl phosphorazidate: Phosphorazidic acid, diphenyl ester (8,9); (26386-88-9)

Cycloundecanecarboxylic acid (8,9); (4373-07-3)

Cyclododecanone (8,9); (830-13-7)

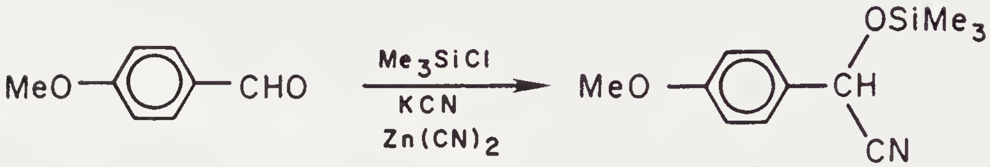
Pyrrolidine (8,9); (123-75-1)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF_3) (1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

In Situ CYANOSILYLATION OF CARBONYL COMPOUNDS:

O-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE

(Benzeneacetonitrile, 4-methoxy-α-[(trimethylsilyl)oxy]-)



Submitted by J. K. Rasmussen and S. M. Heilmann[1].

Checked by M. F. Semmelhack and Raj N. Misra.

1. Procedure

Caution! Potassium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a nitrogen-inlet tube, and a rubber septum (Note 1) are placed 97.5 g (1.5 mol) of finely ground potassium cyanide (Note 2), 81.4 g (0.75 mol, 95.2 mL) of chlorotrimethylsilane (Note 3), 68 g (0.5 mol) of p-anisaldehyde (Note 4), 100 mL of dry acetonitrile (Note 5) and 0.5 g (4.25 mmol) of zinc cyanide (Note 6). The reaction mixture is blanketed with dry nitrogen (Note 7), stirring is begun, and the temperature is raised (heating mantle) to maintain gentle reflux. Heating is continued under these conditions for 30 hr (Note 8), with the occasional removal of small samples by syringe for monitoring by GLC (Note 9). Upon completion of the reaction, the mixture is cooled to ambient temperature and filtered. The filter cake is washed twice with 50 mL of dry acetonitrile and the combined filtrates are concentrated on a rotary evaporator. The residue is distilled at reduced pressure (Note 10). The yield of the colorless liquid (Note 10), which boils at 93-98°C (0.15 mm), amounts to 105-115 g (90-98% based on p-anisaldehyde).

2. Notes

1. All glassware was oven-dried overnight at 130°C, assembled hot, and allowed to cool under a flow of dry nitrogen.

2. Reagent grade potassium cyanide was purchased from Matheson, Coleman and Bell, and dried at 115°C (0.5 mm) for 24 hr. The checkers found it necessary to use newly purchased potassium cyanide. The use of potassium cyanide which was several years old gave incomplete reaction even at extended reaction times. The large excess of potassium cyanide is used simply to obtain convenient reaction times. For comparison, use of 1.5 equiv of KCN gave 38% conversion under conditions where 3 equiv produced 100% conversion.

3. Chlorotrimethylsilane was supplied by Petrarch Systems, Inc., and used without further purification.

4. p-Anisaldehyde, 95%, (4-methoxybenzaldehyde) was used as supplied by Aldrich Chemical Co.

5. Acetonitrile, 99%, supplied by Aldrich Chemical Co., was dried over Linde type 4Å molecular sieves for 12 hr and decanted.

6. Technical grade zinc cyanide was used as supplied by Matheson, Coleman and Bell. Other Lewis acids, notably aluminum chloride, zinc bromide, and zinc iodide may be used as catalysts for the reaction.

7. To "blanket with nitrogen," the checkers simply prepared the reaction mixture with the flask open, introduced a flow of nitrogen over the surface for a few minutes, and then closed the system with an exit through a mercury bubbler to maintain a positive pressure.

8. The reaction time required depends on the catalyst. Zinc iodide, zinc cyanide, and zinc bromide produce essentially complete conversion under these conditions in approximately 16.5, 28 and 30 hr, respectively, probably reflecting solubility differences. When zinc iodide is used, the distilled product is often colored because of the formation of small amounts of iodine.

9. This may be done using a simple boiling point column. We have employed either 10% UCW-98 on Chromosorb W or SP-2100 on 80/100 Supelcoport G2642. The checkers did not monitor the reaction except to extract a small sample after 30 hr in order to verify the absence of starting aldehyde by ^{1}H NMR spectroscopy.

10. Distillation should be below 100°C. In some instances, at distillation temperatures in excess of 100°C, reversion to the starting aldehyde and trimethylsilyl cyanide has been observed. The pure compound shows the following spectral data: ^{1}H NMR (CCl_4): δ 0.28 (s, 9 H), 3.86 (s, 3 H), 5.35 (s, 1 H), 6.83 (d, J = 9, 2 H), 7.35 (d, J = 9 , 2 H); IR (film) cm^{-1}: 2965, 1614, 1512, 1258, 1180, 1089, 878, 850. The purity of the crude product is generally such that a distillation forecut need not be taken.

3. Discussion

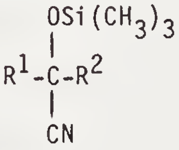
Cyanosilylations have generally been accomplished by addition of a trialkylsilyl cyanide to the corresponding aldehyde or ketone.[2-5] Although this method is straightforward and proceeds in good to excellent yield, use of preformed trialkylsilyl cyanides has a number of disadvantages, particularly when one considers larger scale preparations. Trialkylsilyl cyanides can be prepared[6] by treatment of the corresponding silyl chlorides either with silver cyanide or with lithium cyanide generated in situ by reaction of lithium hydride with hydrogen cyanide. The former procedure involves the use of stoichiometric quantities of a rather expensive reagent, while the latter involves handling fairly large quantities of hydrogen cyanide gas. In addition, both procedures require relatively long reaction times, distillation of the silyl cyanide, and produce only moderate to good yields. More recently, improved syntheses of trimethylsilyl cyanide have appeared.[7,8] Commercially available trimethylsilyl cyanide is also rather expensive.

Silylated cyanohydrins have also been prepared via silylation of cyanohydrins themselves[9] and by the addition of hydrogen cyanide to silyl enol ethers.[10] Silylated cyanohydrins have proved to be quite useful in a variety of synthetic transformations, including the regiospecific protection of p-quinones,[11] as intermediates in an efficient synthesis of α-aminomethyl alcohols,[6] and for the preparation of ketone cyanohydrins themselves.[12] The silylated cyanohydrins of heteroaromatic aldehydes have found extensive use as acyl anion equivalents, providing general syntheses of ketones[13] and acyloins.[14]

The in situ cyanosilylation of p-anisaldehyde is only one example of the reaction which can be applied to aldehydes and ketones in general.[15] The simplicity of this one-pot procedure coupled with the use of inexpensive reagents are important advantages over previous methods. The silylated cyanohydrins shown in the Table were prepared under conditions similar to those described here. Enolizable ketones and aldehydes have a tendency to produce silyl enol ethers as by-products in addition to the desired cyanohydrins. The problem can be overcome by using a modified procedure in which dimethylformamide is employed as solvent.[15]

TABLE

In Situ CYANOSILYLATION OF CARBONYL COMPOUNDS

 $R^1\text{-}\overset{\overset{\textstyle OSi(CH_3)_3}{|}}{\underset{\underset{\textstyle CN}{|}}{C}}\text{-}R^2$	Distilled Yield (%)	Bp. (°C) (pressure, mm)
$R^1 = C_6H_5$, $R^2 = H$	95-98	93-95 (1.75)
$R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$	91	87 (0.45)
$R^1 = 2\text{-}ClC_6H_4$, $R^2 = H$	99	92-93 (0 45)
$R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$	93	100 (0.45)
$R^1 = C_6H_5$, $R^2 = CH_3$	93	73-75 (0.9)
$R^1, R^2 = (CH_2)_5$	89	96 (15)
$R^1 = c\text{-}C_6H_{11}$, $R^2 = H$	87	106-108 (6.5)

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

O-Trimethylsilyl-4-methoxymandelonitrile: Benzeneacetonitrile, 4-methoxy-α-[(trimethylsilyl)oxy]- (10); (66985-48-6)

Potassium cyanide (8,9); (151-50-8)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

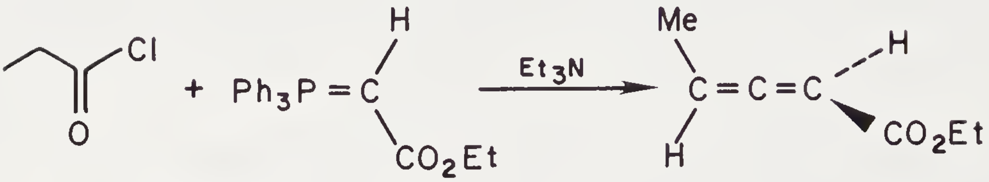
p-Anisaldehyde (8); Benzaldehyde, 4-methoxy- (9); (123-11-5)

Zinc cyanide (8,9); (557-21-1)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl- (8,9); (7677-24-9)

α-ALLENIC ESTERS FROM α-PHOSPHORANYLIDENE ESTERS AND ACID CHLORIDES: ETHYL 2,3-PENTADIENOATE

(2,3-Pentadienoic acid, ethyl ester)



Submitted by Robert W. Lang[1a] and Hans-Jurgen Hansen[1b].

Checked by William F. Burgoyne and Robert M. Coates.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a nitrogen inlet, a 250-mL, pressure-equalizing dropping funnel fitted with a gas outlet, and a Teflon-coated magnetic stirring bar. The flask is charged with 300 mL of dichloromethane (Note 1) and 34.8 g (0.10 mol) of ethyl (triphenylphosphoranylidene)acetate (Note 2) and flushed with nitrogen. The yellow solution is stirred at 25°C as a solution of 10.1 g (0.10 mol) of triethylamine (Note 3) in 100 mL of dichloromethane is added dropwise over 5 min. After 10 min, 9.25 g (0.10 mol) of propionyl chloride (Note 4) in 100 mL of dichloromethane is added dropwise to the vigorously stirred solution over 15 min (Note 5). Stirring is continued for an additional 0.5 hr (Note 6) after which the clear, yellow-tinted mixture is evaporated on a rotary evaporator at reduced pressure using a water bath maintained at 25°C (Note 7). A 500-mL portion of pentane (Note 8) is added to the semi-solid residue, and the slurry is allowed to stand for 2 hr while it is shaken periodically to facilitate solidification and to complete the extraction of the product. The precipitate is removed by filtration through a coarse, sintered-glass Buchner funnel, and the filter cake is washed with a 50-mL portion of pentane. The filtrates are combined and concentrated at reduced pressure to approximately one-fourth of the original volume using a water bath maintained at 25°C. The mixture is filtered again to remove triphenylphosphine oxide, and the remaining solvent is then evaporated. Rapid distillation of the residual liquid in a short-path distillation apparatus under reduced pressure (Note 9) affords a small forerun amounting to 0.5 mL or less and 7.8-8.1 g (62-64%) of ethyl 2,3-pentadienoate, bp 57-59°C (12-14 mm) (Notes 10 and 11).

2. **Notes**

1. Dichloromethane was purified by percolation through Woelm activity grade 1 basic alumina and stored under nitrogen.

2. Ethyl (triphenylphosphoranylidene)acetate is available from Fluka AG and Tridom Chemical Inc. under the name (ethoxycarbonylmethylene)triphenylphosphorane and from Aldrich Chemical Company, Inc. under the name (carbethoxymethylene)triphenylphosphorane. The reagent may be prepared from triphenylphosphine and ethyl bromoacetate by the following procedure.[2]

A 1-L, two-necked, round-bottomed flask fitted with a dropping funnel and a mechanical stirrer is charged with 131.0 g (0.5 mol) of triphenylphosphine (Fluka AG, purum) and 250 mL of benzene (Merck, pro analysi). The solution is stirred vigorously while 83.5 g (0.5 mol) of ethyl bromoacetate (Fluka AG, practical grade) is added dropwise at a rate that maintains the reaction mixture at, or slightly above, room temperature. After a total of 2 hr the reaction is complete and the colorless phosphonium salt is filtered. The salt is washed with 300 mL of cold benzene and 200 mL of pentane and then dissolved in 3 L of water at room temperature. Some further organic impurities are removed by extraction with ether after which 2 drops of 2% alcoholic phenolphthalein are added. The aqueous solution is stirred vigorously and cooled in an ice bath as 2 M aqueous sodium hydroxide is added slowly until the pink endpoint is reached (pH 8-10). The crystalline phosphorane is collected by filtration, washed thoroughly with cold water, and dried, first with a rotary evaporator under reduced pressure at 60°C and then overnight in a drying oven at 180 mm and 70°C. The white to cream-colored crop of ethyl (triphenylphosphoranylidene)acetate, mp 124-126°C, weighs 150-156 g (86-90%) and may be used for the preparation of α-allenic esters without further purification.

3. Triethylamine was supplied by Fluka AG and Aldrich Chemical Company, Inc.

4. Propionyl chloride was purchased from Fluka AG and Aldrich Chemical Company, Inc. and was freshly distilled at 78-80°C (760 mm) prior to use.

5. The checkers maintained the temperature of the reaction mixture at ca. 25°C by cooling with a water bath during the addition of propionyl chloride.

6. The progress of the reaction may be followed by analytical thin-layer chromatography on alumina. The submitters used polygram pre-coated plastic sheets (Alox N/UV$_{254}$) purchased from Macherey-Nagel, Inc. The plates were developed with 1:1 hexane-ether and stained with basic permanganate. The R_f of the product is 0.56.

7. For the isolation of relatively volatile α-allenic esters such as ethyl 2,3-pentadienoate, the submitters recommend that the rotary evaporation be carried out with cooling in an ice bath. When this precaution was taken, the submitters obtained 8.5-9.5 g (67-75%) of product after distillation.

8. The checkers dried the pentane over sodium wire prior to use.

9. The checkers stirred the distilling liquid rapidly with a magnetic stirrer and maintained a bath temperature of 75-85°C throughout the distillation.

10. Ethyl 2,3-pentadienoate has the following spectral properties: IR (thin film) cm^{-1}: 1965, 1720, 1410, 1250, 1025, 865, 790; ^1H NMR (CCl_4) δ: 1.26 (t, 3 H, J = 7, OCH_2CH_3), 1.78 (m, 3 H, CH_3), 4.11 (q, 2 H, J = 7, OCH_2CH_3), 5.28-5.68 (m, 2 H, at C-2 and C-4).

11. On 0.01-mol scale the yield of ethyl 2,3-pentadienoate is 0.79-0.93 g (64-74%). The product was purified by bulb-to-bulb distillation with a Kugelrohr apparatus at 12-14 mm with an oven temperature at 75-85°C.

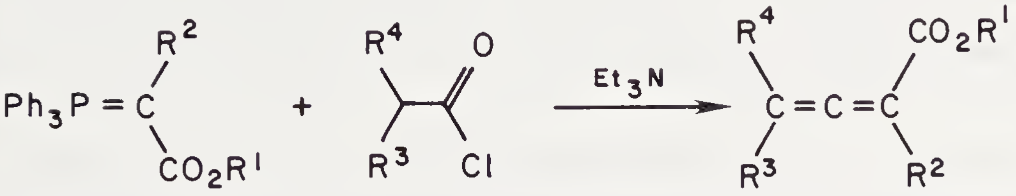
3. Discussion

The acylation of Wittig reagents provides the most convenient means for the preparation of allenes substituted with various electron-withdrawing substituents.[3] The preparation of α-allenic esters has been accomplished by the reaction of resonance-stabilized phosphoranes with isolable ketenes[4-9] and ketene itself[10] and with acid chlorides in the presence of a second equivalent of the phosphorane.[5] The disadvantages of the first method are the necessity of preparing the ketene and the fact that the highly reactive mono-substituted ketenes evidently cannot be used. The second method fails when the α-carbon of the phosphorane is unsubstituted.[11]

The present procedure affords a general method for preparing α-allenic esters (Table I) which avoids the limitations of the previous methods.[12] Thus, α-allenic esters unsubstituted at C-2 are now available in generally satisfactory yields. Ethyl 2,3-pentadienoate, the title compound, had not been prepared prior to the development of this procedure by the submitters. The mild conditions, (i.e., room temperature for relatively short times), avoid the base-catalyzed isomerization of the conjugated allenes to acetylenes.[13] The corresponding phosphonium salts may also be used directly in the reaction provided two equivalents of triethylamine are employed, obviating the lengthy process for drying the phosphorane.[14] Dichloromethane and acetonitrile have been used as solvents for the reaction.[12] The α-allenic esters are usually obtained in analytically pure form after bulb-to-bulb distillation. They may also be purified by column chromatography on alumina with 9:1 hexane-ether as eluant.[14]

TABLE I

PREPARATION OF α-ALLENIC ESTERS BY THE WITTIG-REACTION[12]



R^1	R^2	R^3	R^4	Solvent	Procedure[a]	Yield(%)
CH_3	H	H	H	CH_2Cl_2	A	40
C_2H_5	H	$(CH_3)_3C$	H	CH_3CN	B	55
CH_3	H	C_6H_5	H	CH_3CN	B	23
C_2H_5	CH_3	H	H	CH_2Cl_2	A	59
C_2H_5	CH_3	CH_3	H	CH_2Cl_2	A	74
C_2H_5	CH_3	CH_3	CH_3	CH_2Cl_2	B	39
CH_3	CH_3	$(CH_3)_3C$	H	CH_3CN	B	66
C_2H_5	CH_3	C_6H_5	H	CH_2Cl_2	A	70

[a] The reaction times varied from 10 min to 18 hr. A=the corresponding phosphonium salt was used with the addition of two moles of triethylamine. B=the corresponding phosphorane was used with the addition of one mole of triethylamine.

The submitters have shown that these reactions proceed by dehydrochlorination of the acid chloride to the ketene, which is then trapped by reaction with the phosphorane. The resulting betaine decomposes to the -allenic ester via an oxaphosphetane. In contrast, the reaction of acid chlorides with 2 equivalents of phosphoranes involves initial acylation of the phosphorane followed by proton elimination from the phosphonium salt.[5]

1. (a) Zentrale Forschungslaboratorien, CIBA-Geigy AG, Postfach CH-4002, Basel, Switzerland. (b) Zentrale Forschungseinheiten, F. Hoffmann-La Roche & Co. AG, Postfach, CH-4002 Basel, Switzerland. Work done at the Institute of Organic Chemistry, University of Fribourg, CH-1700 Fribourg, Pérolles, and supported by the Swiss National Science Foundation.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

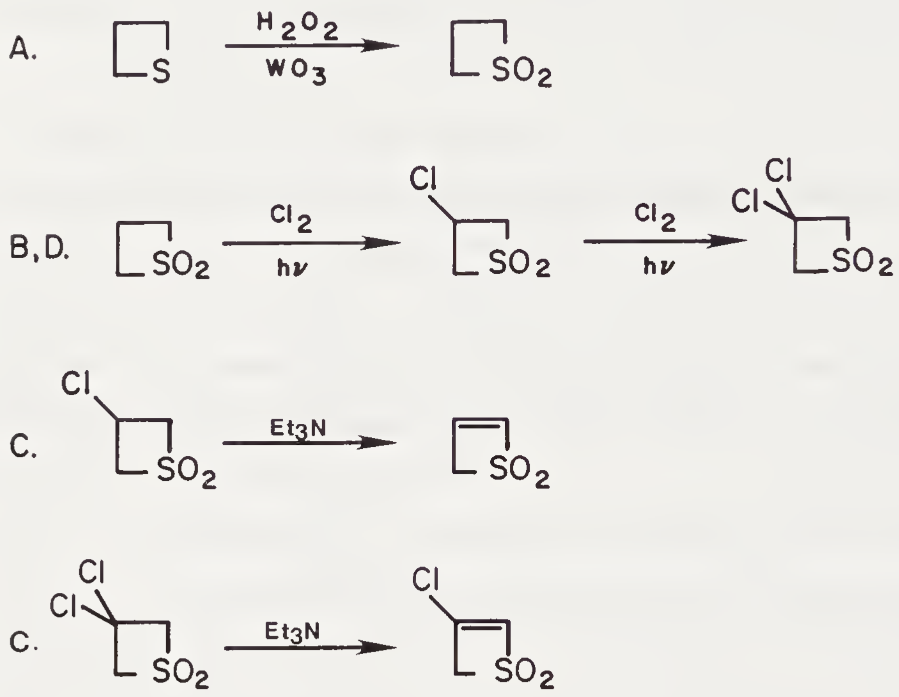
(Carbethoxymethylene)triphenylphosphorane, (Ethoxycarbonylmethylene)triphenylphosphorane: Acetic acid, (triphenylphosphoranylidene)-, ethyl ester (8,9); (1099-45-2)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

THIETE 1,1-DIOXIDE AND 3-CHLOROTHIETE 1,1-DIOXIDE

(2H-Thiete 1,1-dioxide and 2H-thiete, 3-chloro- 1,1-dioxide)



Submitted by Thomas C. Sedergran and Donald C. Dittmer[1].

Checked by M. F. Semmelhack, Elena M. Bingham, William A. Sheppard, and Joseph J. Bozell.

1. Procedure

A. Thietane 1,1-dioxide. The pH of a solution of tungstic acid ($WO_3 \cdot H_2O$) (1.1 g, 0.044 mol) (Note 1) in 280 mL of distilled water is adjusted to 11.5 by addition of 10% aqueous sodium hydroxide; the white suspension of the tungstate catalyst is added to a 1-L, round-bottomed flask fitted with a mechanical stirrer and a pressure-equalizing addition funnel. The tungstic acid-water mixture is cooled to 0-10°C by means of an ice-salt bath; glacial acetic acid (50 mL) and trimethylene sulfide (thietane) (47.5 g, 0.641 mol, d 1.028) (Note 2) are added. The chilled mixture is stirred, and 30% hydrogen peroxide (189 mL) is added carefully by means of the addition funnel over a period of 2 hr (Note 3). The mixture is stirred at 0-10°C for an additional hour, transferred to an evaporating dish and heated to near dryness on a steam bath. The resulting solid material is triturated five times with 100-mL portions of hot chloroform, any catalyst being removed by filtration. The chloroform solutions are combined, dried over anhydrous magnesium sulfate and the solvent removed via a rotary evaporator to give a white solid (60.3-63.7 g, 0.57-0.60 mol, 88.7-93.7%), mp 74-76°C (lit[2] mp 75.5-76°C).

B. 3-Chlorothietane 1,1-dioxide. Thietane 1,1-dioxide (14.0 g, 0.132 mol) is placed in a three-necked, 500-mL, round-bottomed flask fitted with a magnetic stirrer, reflux condenser and a chlorine bubbler. (*Caution! Since chlorine is poisonous, the reaction involving it should be done in a good hood.*) Carbon tetrachloride (300 mL) is added to the flask (Note 4) and the suspension is irradiated by a 250-watt sunlamp positioned as close as possible to the reaction flask without touching it (Note 5) while chlorine is bubbled through the solution for 15 min at a moderate rate (Note 6). A copious white precipitate forms and irradiation and addition of chlorine must be stopped at this point (or 10 min after the first appearance of a precipitate) to avoid dichlorination. The reaction mixture is cooled to room temperature and filtered to give a white, fluffy product (5.4-8.1 g, 30-44%) which is crystallized from chloroform, mp 136-137°C (lit[3] mp 136.5-137.5°C).

C. Thiete 1,1-dioxide. A sample of 3-chlorothietane 1,1-dioxide (8.0 g, 0.057 mol) is dissolved in dry toluene (300 mL) (Note 7) in a 500-mL, two-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, heating mantle (or silicone oil bath), and thermometer. The reaction is heated to 60°C and triethylamine (28.7 g, 0.28 mol, 39.5 mL) is added through the condenser. The reaction mixture is stirred for 4 hr and triethylamine hydrochloride is removed by filtration and washed with toluene (100 mL). Toluene is removed on a rotary evaporator and the residue is recrystallized from diethyl ether-ethanol (Note 8) to give a white solid (4.5-4.8 g, 75-81%); mp 49-50°C (lit[3] mp 52-54°C).

D. 3,3-Dichlorothietane 1,1-dioxide. Thietane 1,1-dioxide (5.0 g, 0.047 mol) is placed in a 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and chlorine gas bubbler. Carbon tetrachloride (350 mL) is added and the solution is irradiated with a 250-watt sunlamp (Note 5) while chlorine is bubbled through the stirred mixture for 1 hr (Note 9). Irradiation and chlorine addition are stopped and the reaction mixture is allowed to cool to room temperature. The product is collected by filtration as a white solid (4.0-4.4 g, 49-53%), mp 156-158°C (Note 10). The product can be used without further purification or it can be recrystallized from chloroform.

E. 3-Chlorothiete 1,1-dioxide. A solution of 3,3-dichlorothietane 1,1-dioxide (4.0 g, 0.023 mol) in toluene (150 mL) is placed in a 250-mL, round-bottomed, two-necked flask equipped with a heating mantle (or silicone oil bath), magnetic stirrer, reflux condenser, and thermometer. The solution is heated to 60°C and triethylamine (2.54 g, 0.025 mol, 3.5 mL) is added dropwise through the condenser over a 10-min period. The solution is stirred for 2 hr at 60°C and cooled to room temperature. The triethylamine hydrochloride is collected by filtration and washed with hot toluene (50 mL). Removal of toluene on a rotary evaporator gives a white solid (2.7-3.0 g, 84-93%) which is recrystallized from chloroform-hexane, mp 118-120° (Note 11).

2. Notes

1. The tungstic acid was used as supplied by the Eastman Kodak Company.

2. The trimethylene sulfide was used as supplied by the Aldrich Chemical Company.

3. The addition rate of the hydrogen peroxide must be adjusted so that the temperature of the reaction mixture does not rise above 10°C. The yield is reduced if the temperature is allowed to rise above that point. The end point of the reaction, when excess peroxide is present, can be determined with potassium iodide - starch test paper. The yield also is reduced if more than a slight excess of hydrogen peroxide is used.

4. The sulfone is not completely dissolved at this point. The prescribed ratio of sulfone to carbon tetrachloride (0.0467 g mL) is important. If it is less (i.e., more carbon tetrachloride relative to sulfone), considerable 3,3-dichlorothietane 1,1-dioxide will be formed.

5. Any commercial sunlamp is satisfactory and should be used with eye protection. Carbon tetrachloride boils gently because of the heat from the lamp.

6. The submitters suggested adding the chlorine at such a rate that a constant yellow color is maintained in the solution or suspension. The checkers found that, depending on the rate of chlorine introduction, it took from 10 to 35 min for the appearance of the white precipitate. In each run, the monochlorinated product was contaminated with a small amount (5-10% by NMR integration) of either starting material or dichlorinated product. The checkers found that the optimum yield of monochlorinated product was obtained when the chlorine was bubbled into the solution through a 1/4" glass tube at a rate estimated to be between 5-15 bubbles per sec. The suspended sulfone dissolves as the reaction proceeds.

7. Toluene was dried over 4Å molecular sieves. Benzene may be used also.

8. The product is heated in about 25-30 mL of diethyl ether, and ethanol is added dropwise until a solution is obtained. The checkers found that the thiete could also be crystallized by gently heating the crude material in diethyl ether (~100 mL) until it dissolves, followed by cooling to -15°C.

9. If the reaction time is less than 1 hr, a mixture of monochloro- and dichlorosulfone is obtained.

10. The spectral properties of the product are as follows: IR (KBr disc) cm^{-1}: 2950 (m), 1370 (m, SO_2), 1310 (m), 1210 (m), 1140 (m, SO_2), 970 (m), 940 (m), 820 (w); ^1H NMR (chloroform-d) δ: 5.0 (s, 4 H, $CH_2SO_2CH_2$). Anal. Calcd. for $C_3H_4Cl_2O_2S$: C, 20.70; H, 2.30. Found: C, 20.81; H, 2.39.

11. The spectral properties of the product are as follows: IR (KBr disc) cm^{-1}: 1540 (m, >C=C<), 1400 (w), 1300 (s, SO_2), 1210 (s), 1140 (s, SO_2), 1020 (m), 770 (m); ^1H NMR (chloroform-d) δ: 6.8 (s, 1 H, CH=C), 4.6 (s, 2 H, CH_2-SO_2). Anal. Calcd. for $C_3H_3ClO_2S$: C, 26.00; H, 2.17. Found: C, 25.78; H, 2.02.

3. Discussion

This preparation of thiete 1,1-dioxide is more direct and less tedious than previous methods.[3,4,5]

Oxidation of trimethylene sulfide catalyzed by tungstic acid[6] is preferred to the uncatalyzed reaction: Yields are better and the reaction time is shortened by elimination of an induction period.

Selective chlorination of the 3-position of thietane 1,1-dioxide may be a consequence of hydrogen atom abstraction by a chlorine atom. Such reactions of chlorine atoms are believed to be influenced by polar effects, preferential hydrogen abstraction occurring remotely from an electron withdrawing group.[7] The free radical chain reaction may be propagated by attack of the 3-thietanyl 1,1-dioxide radical on molecular chlorine.

Conversion of 3-chlorothietane 1,1-dioxide to the 3-(N,N-dimethylamino) derivative followed by reduction, quaternization, and Hofmann elimination affords a convenient route to the highly reactive thiete (thiacyclobutene).[4,8]

The following compounds have been obtained from thiete 1,1-dioxide: Substituted cycloheptatrienes,[9] benzyl α-toluenethiosulfinate,[10] pyrazoles,[11] naphthothiete 1,1-dioxides,[12] and 3-substituted thietane 1,1-dioxides.[13] It is a dienophile in Diels-Alder reactions[9,12,14] and undergoes cycloadditions with enamines, dienamines, and ynamines.[15] Thiete 1,1-dioxide is a source of the novel intermediate, vinylsulfene ($CH_2=CHCH=SO_2$), which undergoes cycloadditions to strained olefinic double bonds,[16] reacts with phenol to give allyl sulfonate derivatives[17] or cyclizes unimolecularly to give an unsaturated sultene.[17] Platinum[18] and iron[19] complexes of thiete 1,1-dioxide have been reported.

3-Chlorothiete 1,1-dioxide is a potentially useful intermediate for the preparation of other 3-substituted thiete 1,1-dioxides via addition-elimination reactions.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Thiete 1,1-dioxide: 2H-Thiete 1,1-dioxide (9); (7285-32-7)

Thietane 1,1-dioxide (9); (5687-92-3)

Tungstic acid (8,9); (7783-03-1)

Trimethylene sulfide (8); Thietane (9); (287-27-4)

3-Chlorothietane 1,1-dioxide: Thietane, 3-chloro- 1,1-dioxide (8,9); (15953-83-0)

Unchecked Procedures

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2230* Trifluoroacetyl Triflate
S. L. Taylor, T. R. Forbus, Jr. and J. C. Martin, Box 43, Roger Adams Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL 61801

2234* Yeast Reduction of Ethyl Acetoacetate: (*S*)-(+)-Ethyl 3-Hydroxybutanoate
D. Seebach, M. A. Sutter, R. H. Weber, and M. F. Züger, Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Universitätstr 16, CH-8006, Zürich, Switzerland

2235R* 2,2':6',2"-Terpyridine
K. T. Potts, P. Ralli, G. Theodoridis, and P. Winslow, Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12181

2237* Addition of an Ethylcopper Complex to 1-Octyne: (4*E*)-5-Ethyl-1,4-Undecadiene
R. S. Iyer and P. Helquist, Department of Chemistry, State University of New York at Stony Brook, Long Island, NY 11794

2238* Esterification of Carboxylic Acids with Dicyclohexylcarbodiimide/4-Dimethylaminopyridine: *tert*-Butyl Ethylfumarate
B. Neises and W. Steglich, Institut für Organische und Biochemie, Universität Bonn, Gerhard-Domagk-Strasse 1, D-5300 Bonn 1, Federal Republic of Germany

2239* Indoles from 2-Methylnitrobenzenes by Condensation with N,N-Dimethylformamide Acetals and Reduction: 4-Benzyloxyindole
A. D. Batcho and W. Leimgruber, Research Division, Hoffmann - La Roche Inc., Nutley, NJ 07110

2241* Formyl Transfer to Grignard Reagents: 3-Phenylpropionaldehyde
G. A. Olah and M. Arvanaghi, Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA 90007

2243 Cyclobutene
J. Salaün and A. Fadel, Universite de Paris-Sud, 91405 Orsay Cedex, France

2244 Preparation of "Geminal Aminoamides" [*N*-(1-Aminoalkyl)Amides]: *N*-(1-Aminoisobutyl)Acetamide
N. M. Gray, M. R. Almond and G. M. Loudon, Department of Medicinal Chemistry and Pharmacognosy, Purdue University, W. Lafayette, IN 47907

2245* Hexafluoroacetone
M. Van Der Puy and L. G. Anello, Allied Chemical, Buffalo Research Laboratory, 20 Peabody Street, Buffalo, NY 14210

2246* Tris(Dimethylamino) Sulfonium Difluorotrimethylsilicate
W. J. Middleton, E. I. duPont deNemours and Co., Central Research and Development Department, Experimental Station, Wilmington, DE 19898

2248R* 2,3-O-Isopropylidene-D-Erythronolactone
N. Cohen and B. L. Banner, Department of Chemical Research, Hoffmann - La Roche Inc., Nutley, NJ 07110

2249* (S)-(+)-2-(p-Tolylsulfinyl)-2-cyclopentenone
M. Hulce, J. P. Mallamo, L. L. Frye, T. P. Kogan, and G. H. Posner, Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218

2250* 2-Methyl-2-Trimethylsilyloxypentan-3-one
S. D. Young, C. T. Buse and C. H. Heathcock, Department of Chemistry, University of California, Berkeley, CA 94720

2251* (2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic Acid
B. Bal, C. T. Buse and C. H. Heathcock, Department of Chemistry, University of California, Berkeley, CA 94720

2252* (2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic Acid
S. H. Montgomery, M. C. Pirrung and C. H. Heathcock, Department of Chemistry, University of California, Berkeley, CA 94720

2253* Diethyl [(2-Tetrahydropyranyloxy)methyl]phosphonate
A. F. Kluge, Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304

2255* (-)-Isopinocampheol
C. F. Lane and J. J. Daniels, Aldrich-Boranes, Inc., Route 3, Sheboygan, Falls, WI 53085

2259 Geminal Acylation-Alkylation at a Carbonyl Center using Diethyl N-Benzylideneaminomethylphosphonate: Preparation of 2-Methyl-2-phenyl-4-pentenal
S. K. Davidsen, G. W. Phillips, and S. F. Martin, Department of Chemistry, The University of Texas at Austin, Austin, TX 78712

2261* α-Hydroxy Ketones from the Oxidation of Enol Silyl Ethers with m-Chloroperbenzoic Acid
G. M. Rubottom, J. M. Gruber, H. D. Juve, Jr., and D. A. Charleson, Department of Chemistry, University of Idaho, Moscow, ID 83843

2262* Asymmetric Hydroboration of 5-Substituted Cyclopentadienes: Synthesis of Methyl (2R,5R)-5-Hydroxy-2-cyclopentene-1-acetate
J. J. Partridge, N. K. Chadha and M. R. Uskokovic, Department of Natural Products Chemistry, Hoffmann - La Roche Inc., Nutley, NJ 07110

2266 Monoaza-18-crown-6
H. Maeda, Y. Nakatsuji and M. Okahara, Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka, Japan 565

2268* Asymmetric Reduction of α,β-Acetylenic Ketones with B-3-Pinanyl-9-borabicyclo[3.3.1]nonane: (R)-(+)-1-Octyn-3-ol
M. M. Midland and R. S. Graham, Department of Chemistry, University of California, Riverside, CA 92521

2270 A Convenient Preparation of Ethyl 4-Hydroxycrotonate
A. S. Kende and P. Fludzinski, Department of Chemistry, University of Rochester, Rochester, NY 14627

2271* (E)-Buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene. Conversion of Methyl Ketones into Terminal Alkynes
E.-i. Negishi, A. O. King and J. M. Tour, Department of Chemistry, Purdue University, W. Lafayette, IN 47907

2272* (+)-(7aS)-2,3,7,7a-Tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione
Z. G. Hajos and D. R. Parrish, 65 Shady Brook Lane, Princeton, NJ 08540

2273* Asymmetric Hydrogenation of Ketopantoyl Lactone: D-(-)-Pantoyl Lactone
I. Ojima, T. Kogure and Y. Yoda, Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

2274* (+)-Diethyl (2S,3R)-3-Allyl-2-hydroxysuccinate from (-)-Diethyl (S)-malate. Diastereoselective α-Alkylation of β-Hydroxycarboxylic Esters through Alkoxide-enolates
D. Seebach, J. Aebi and D. Wasmuth, Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Universitätstr 16, CH-8006, Zürich, Switzerland

2275* Stereocontrolled Iodolactonization of Acyclic Olefinic Acids: The *Trans* and *Cis* Isomers of 4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-Furanone
F. B. Gonzàlez and P. A. Bartlett, Department of Chemistry, University of California, Berkeley, CA 94720

2276* Hydroxylation of Enolates with MoO_5•Py•HMPA(MoOPH); 1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one
E. Vedejs and S. Larsen, Department of Chemistry, University of Wisconsin, Madison, WI 53706

2277* Ethyl Isocrotonate
M. J. Taschner, T. J. Rosen and C. H. Heathcock, Department of Chemistry, University of California, Berkeley, CA 94720

2278 Vinylation of Enolates with a Vinyl Cation Equivalent: *trans*-3-Methyl-2-vinylcyclohexanone
T. C. T. Chang, M. Rosenblum and N. Simms, Department of Chemistry, Brandeis University, Waltham, MA 02254

2279* Ozonolytic Cleavage of Cyclohexene to Terminally Differentiated Products: Methyl 6-Oxohexanoate, 6,6-Dimethoxyhexanal, Methyl 6,6-Dimethoxyhexanoate
R. E. Claus and S. L. Schreiber, Department of Chemistry, Yale University, New Haven, CT 06511

2282* Stereospecific Reduction of Propargyl Alcohols: (E)-3-Trimethylsilyl-2-propen-1-ol
T. K. Jones and S. E. Denmark, Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, IL 61801

2284R* Valinol
G. A. Smith and R. E. Gawley, Department of Chemistry, P.O. Box 249118, University of Miami, Coral Gables, FL 33124

2285* 2-Alkenylcarbinols from 2-Haloketones: 2-E-Propenylcyclohexanol
P. A. Wender, D. A. Holt and S. McN. Sieburth, Department of Chemistry, Stanford University, Stanford, CA 94305

2286 Dialkoxyacetylenes: Di-*tert*-Butoxyethyne, a Valuable Synthetic Intermediate
A. Bou, M. A. Pericas, A. Riera, and F. Serratosa, Department de Química, Orgànica Facultat de Química, Universitat de Barcelona, Diagonal 647, Barcelona - 28, Spain

2287* Conversion of Epoxides to β-Hydroxy Isocyanides. Trans-2-Isocyanocyclohexanol
P. G. Gassman and T. L. Guggenheim, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

2288 Methylenation of Esters - The Synthesis of Enol Ethers
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The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature. Both are accompanied by its registry number in brackets. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

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